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Editorial

Life at a price: the implantable defibrillator

Electrical reversion of ventricular fibrillation has a long and fascinating history. Kouwenhoven, Zoll, Lown, and Pantridge through their contribution to defibrillator development have saved countless lives, but they did not foresee the automatic implantable defibrillator. For years, Michel Mirowski battled against problems, some technical others political, to develop a reliable automatic implantable defibrillator.[1] Its initial acceptance into clinical practice in the United States was uncharacteristically cautious. Doubts were raised about reliability, longevity, and implantability (the unit weighs up to 250 g with a volume of 145 ml). Rumours were broadcast of runaway defibrillators, bystander shocks, swimming pool hazards, and resistance to external defibrillation. Ten years after the first human implantation, the success of the new generation implantable defibrillators is silencing the critics. Over 10 000 units have been implanted world wide, most in the United States, for a broad and at times remarkable range of indications.

The crucial breakthrough in the development of an implantable defibrillator came from establishing that the epicardial energy requirements for defibrillation of the human heart are an order of magnitude less than those for transthoracic defibrillation. None the less, substantial problems had to be overcome to miniaturise a unit capable of delivering scores of 20–35 J shocks. Improved battery and capacitor technology has given a margin of safety but it remains a vital part of the implantation that the epicardial electrode patches through which the shocks are delivered are sited in areas with the lowest possible energy requirements for reliable defibrillation. Modification of electrode characteristics, electrode numbers, shock numbers, and the energy envelope will allow further reductions in energy requirements for defibrillation. Low energy shocks have important advantages. They use less battery power and thereby increase device longevity; they use smaller batteries and capacitors, which reduces the size of the device; and low energy shocks are better tolerated by patients. The electrical benefits of delivering shocks through epicardial patches are offset by the clinical disadvantages of the thoracotomy, albeit limited, needed for their placement. Transvenous defibrillating electrodes are proving an effective alternative to epicardial patches and they reduce the procedure for defibrillator implantation to little more than that required for a permanent pacemaker.

Reliable automatic activation of an implanted defibrillator is both an absolute clinical necessity and a major technical challenge. Failure to detect a ventricular tachycardia may prove fatal whereas inappropriate delivery of a shock during normal rhythm will cause patient distress and could provoke lethal arrhythmias. Arrhythmia sensing usually depends upon the absolute heart rate or the pattern of heart rate change or both. Positive identification of ventricular fibrillation is an ideal that has been attempted with "probability density function" analysis of electrograms.[2] It is based on the principle that during ventricular fibrillation there are no periods of electrical stability corresponding to the isoelectric line in other cardiac arrhythmias. Unfortunately, local electrograms during ventricular fibrillation may not show the disorganised electrical pattern that characterises the surface electrocardiogram. Further, the myocardium sensed may be subject to entry block and therefore will not reflect the rhythm in the rest of the myocardium. Detection of ventricular tachycardia is even more demanding because its rate may overlap with rates seen during sinus tachycardia or atrial fibrillation.[3] Current systems are not perfect, and inappropriate shock delivery (false positive arrhythmia detection) by implantable defibrillators has been reported in up to 14% of patients.[4] Failure to recognise a ventricular tachycardia (false negative) is less common.[3 4]

Implantable cardioverter defibrillators, antiarrhythmic drugs, and surgery all have a role in the management of life threatening ventricular tachycardia. The relative merits of each need to be examined.

Drugs

Drugs used for the control of life threatening ventricular tachycardias are chosen empirically because there are no reliable criteria that predict the profile of responsiveness of a particular ventricular tachycardia. Once selected, the efficacy of treatment should be tested by programmed electrical stimulation.[5] Multiform ventricular tachycardia and ventricular fibrillation pose difficulties. Their control by antiarrhythmic treatment is less certain than for sustained uniform ventricular tachycardia and there is still debate regarding the value of electrophysiological testing because multiform ventricular tachycardia and ventricular fibrillation may be non-specific responses to vigorous stimulation and thus may be indistinguishable from the native event. Medical treatment (electrophysiologically tested) is successful in only 40% of patients with life threatening ventricular tachycardias. For them, continued long term treatment is associated with a 90–95% survival rate and freedom from arrhythmia at one year.[6 7] Those who do not respond and those given empirical antiarrhythmic treatment without electrophysiological confirmation of efficacy, fare much less well (30–50% one year survival and freedom from recurrence). The results of electrophysiological testing of amiodarone may be difficult to interpret but even untested treatment with this agent offers a $\geqslant 80\%$ one year survival and freedom from arrhythmia recurrence.[8] Left ventricular depression and arrhythmogenesis are important unwanted effects of antiarrhythmic drugs that may seriously restrict their use. Other unwanted effects are usually tolerable if the agent prevents life threatening recurrences of arrhythmia.

Operation

Surgical management of ventricular tachycardia has many attractions; it offers the prospect of a cure, allows other corrective surgery (coronary artery bypass grafting etc), and is relatively inexpensive. But operative risks, the specialised nature of the mapping procedures, and problems of postoperative myocardial function are major detractions. Because ventricular fibrillation affects most if not all of the ventricle and does not originate from a circumscribed focus (as does ventricular tachycardia), prospects for surgical treatment of this arrhythmia seemed bleak. New mapping strategies and the development of surgical procedures that raise ventricular fibrillation thresholds may yet extend the usefulness of surgery to this arrhythmia.[9] Ventricular fibrillation caused by ischaemia should be managed by revascularisation—a strategy that is particularly applicable to patients resuscitated from out-of-hospital ventricular fibrillation who have coronary artery disease but have not suffered an acute myocardial infarction. The results of map directed antiarrhythmic operations are varied and patient selection is important to outcome. Operative mortality ranges from 7% to 27%[10] but nearly all survivors (94%) are alive a year later.[9]

Implantable defibrillators

Implantation of a cardioverter defibrillator carries a small risk (1–2% mortality) and even very sick patients, particularly those with severe left ventricular depression, tolerate the procedure well.[3,4,11] Recent efficacy figures indicate a 1% one year and an 8% five year sudden death rate.[4] Manufacturers of the devices not unnaturally tend to quote such statistics but overall mortality figures in the same study (that is, total mortality) are 4% at one year and 26% at five years.[4] In the United States and in parts of Europe, defibrillators are being implanted on a scale beyond belief. A past history of a life threatening ventricular tachycardia or the inability to exclude the risk of such an event in the future may be sufficient to identify candidates for these devices. But many ventricular tachycardias are single unique events that are unlikely to be repeated—for example, when they occur in acute phase infarction. Covering a risk, however small, and offering protection at all costs has a humanitarian appeal but in the United Kingdom these are unrealistic health strategies. Unnecessary implantation is a profligate use of resources and creates falsely optimistic survival figures because patients not at risk of arrhythmic death are counted as defibrillator recipients. Appropriate device discharge is the best endorsement of implantation. Reports that only 58% of patients have received a shock in some series[4] must raise concerns about patient selection. Implantable defibrillators are not without their problems—extrusion, infection, lead problems, arrhythmogenesis (most series report patients in whom new arrhythmias develop or in whom the index arrhythmia becomes more troublesome after implantation), and psychiatric disturbance.[3,4,11,12]

Outlook

What of the future? Implantable cardioverter defibrillator technology will advance. Back up bradycardia pacing, automatic cardioversion/defibrillation selection, antitachycardia pacing, and miniaturisation will be available—but at a price. Competition eventually will drive down costs although the substantial development investment must be recouped in some way. "Hype" and fashion will encourage us to buy the latest technology, which may over-provide for clinical need. Antiarrhythmic surgery will stagnate until the differences between cure and palliation are better appreciated. New antiarrhythmic drugs will appear but they will be better versions of currently available compounds rather than agents with dramatically new features likely to increase the number of patients who respond.

What of the present? The evidence is that automatic implantable defibrillators work. The reality is that their implantation is easy and demands neither great skill nor complex equipment. Defibrillators are already available but they have yet to make an impact in the United Kingdom. The problem is not apathy but rather price. Each unit costs £9000–£13 000, which must be met from current NHS resources, from insurance companies, or from patients themselves. If we are to achieve optimal cost benefit patients must be carefully selected. Yet there are no guidelines for practice in the United Kingdom. Regulatory and professional bodies—the Department of Health, the British Cardiac Society, and the British Pacing and Electrophysiology Group—are aware of the problems and have begun to act; but their initiative seems neither powerful nor rapid. The clinical and budgetary issues are already on our doorstep.

Medicines, surgery, the implantable defibrillator—which is best? The question is unanswerable though some reports suggest the contrary. There have been no randomised studies of these three management strategies and perhaps there never will be. Electrophysiologically tested and proven antiarrhythmic drug treatment that is tolerated by the patient is the best management for the present. This option is badly implemented largely because electrophysiological services are not as well developed as they ought to be. This is unpardonable. Electrophysiological testing for such patients requires only a single temporary right ventricular pacing catheter linked to a simple inexpensive stimulator. The end point—arrhythmia or no arrhythmia—can be determined from a standard electrocardiographic monitor. This management shortcoming can be corrected easily but the real problem is the 60% of patients for whom medical treatment is ineffective or not tolerated. For this population, a randomised study of surgery versus the implantable defibrillator has scientific appeal; yet these options are so radically different. Surgery has a high operative risk but is relatively inexpensive and offers a cure. The defibrillator carries a low implantation risk, is expensive, and offers palliation. The mortality for each treatment is broadly similar. Seen in this light the issue could be decided on the basis of cost or on the basis of the quality of life. In practice, surgery and the implantable defibrillator should not be seen as competitive solutions for the same problem. The optimal application of each must be defined. Yet surprisingly this aspect has been almost completely neglected. Perhaps this is because few centres have embraced both strategies with equal fervour. We must accept that each has a role and identify the arrhythmias and patients to which each is best suited. That done, we can define good clinical practice and can estimate the cost of optimal care. This research can and should be done in the United Kingdom. Interested and worried clinicians are beginning to address the issue but their activities need funding and coordination. The implantable defibrillator will not be the last expensive technical development in cardiology and the United Kingdom needs a reliable, sensitive, rapid, and informed mechanism for evaluating this and similar expensive treatments.

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Br Heart J 1990;64:174–6

REVIEW

Late potentials as predictors of risk after thrombolytic treatment?

Günter Breithardt, Martin Borggrefe, Ulrich Karbenn

Late potentials represent low amplitude fractionated electrical activity and they appear at the end of or after the QRS complex. They can be recorded directly by catheter mapping or intraoperative endocardial and epicardial mapping[1–3] or indirectly from the body surface by "high-resolution electrocardiography"[4–7] after myocardial infarction in patients with sustained ventricular tachycardia. These potentials originate from asynchronous electrical activity in bundles of surviving muscle, mostly at the border of a myocardial infarction. These surviving muscle bundles are separated by fibrous tissue that can form isolating boundaries between them.[8 9] The low amplitude of these signals is probably the result of the large amount of connective tissue and few surviving muscle fibres beneath the electrode.[8] They are considered as markers for an "arrhythmogenic substrate" that may become the site for re-entry.[10] However, not all sites showing late potentials are arrhythmogenic; occasionally they are non-specific markers of local fibrosis.[11]

Late potentials have rarely been seen in patients with normal left ventricular function.[4–7] But they were found in 90% of patients with ventricular tachycardia or ventricular fibrillation after previous myocardial infarction.[6] Late potentials were much less common in patients with previous ventricular fibrillation than in patients with sustained uniform ventricular tachycardia.[6] The longer the duration of late potentials the faster was the rate of ventricular tachycardia. Late potentials were most common in patients with left ventricular aneurysms caused by coronary artery disease and in patients with other abnormalities of left ventricular contraction.[12] Late potentials were more common in patients with inducible ventricular tachycardia.[13]

Late potentials are strong predictors of arrhythmic events after myocardial infarction.[7] This was convincingly shown in more than 2000 survivors of myocardial infarction. The presence of late potentials during recovery from myocardial infarction (detected by the use of high resolution electrocardiography) correlated with the subsequent occurrence of sustained uniform ventricular tachycardia or death from arrhythmia or both.

Clinical reports that showed a correlation between the absence of late potentials after myocardial infarction and the success of thrombolytic treatment are important because they indicate that effective thrombolytic treatment can prevent the development of an abnormal electrophysiological milieu after myocardial infarction.[14–16]

Eldar *et al* reported on the effect of thrombolysis on the evolution of late potentials in the early postinfarction period.[15] A hundred and fifty eight patients were prospectively studied during the first 10 days after acute myocardial infarction. The study population consisted of two non-randomised groups. Ninety three patients had been treated conservatively whereas 65 patients had been treated by intravenous thrombolysis. The incidence of late potentials in the first two days after infarction was not significantly different in patients treated conservatively (14%) and those treated by thrombolysis (11·8%). On days 7–10 the incidence of late potentials among patients treated by thrombolysis was unchanged; however, it had increased significantly in the conservatively treated group from 11·8% to 22·5% ($p < 0·01$). Volosin *et al* also evaluated the time course of late potentials after myocardial infarction.[17] They found that in reperfused infarctions development of late potentials was related to the presence of Q waves and was independent of peak creatine kinase concentrations and infarct location. Late potentials sometimes were present only in the early infarction period; they may represent areas of transiently delayed myocardial activation that resolve with infarct healing.[17]

Gang *et al* reported a similar study in 106 consecutive patients aged <75 years who were admitted to hospital with a first acute myocardial infarction.[14] Forty four patients who had chest pain for less than four hours were treated with alteplase (recombinant tissue plasminogen activator) whereas another 62 patients who either did not qualify for or refused treatment with alteplase were treated conventionally. Thus, they were not a randomised sample of patients with acute myocardial infarction. Age, sex, site, and size of myocardial infarction, extent of coronary artery disease, and left ventricular ejection fraction were similar in both groups. Signal averaging was performed in all patients within 48 hours of admission to the hospital and again in the surviving patients before discharge. Only two (5%) of the 44 patients treated with alteplase had late potentials compared with 14 (23%) of 62 patients who were not ($p = 0·01$). The patency of the infarct-related coronary artery and administration of alteplase were the only independent predictors of the presence of late potentials.

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Preliminary data from Riccio *et al* on 172 patients in the Gruppo Italiano per lo Studia della Streptochinasi nell' Infarto Miocardico (GISSI-2) study point to similar findings.[16] Twenty (16·5%) of 103 patients treated with streptokinase or alteplase had late potentials compared with 17 (28·9%) of 69 patients who did not receive thrombolytic treatment because of contraindications or late admission to the hospital.

Kersschot *et al* used programmed ventricular stimulation with three extrastimuli to test for the presence of an arrhythmogenic substrate.[18] Twenty six days after infarction the induction rate for sustained ventricular arrhythmias in general (48% *v* 100%) and uniform ventricular tachycardia (29% *v* 67%) in particular was much lower in 21 patients treated with intravenous and intracoronary streptokinase than in 15 control patients. But contradictory results were reported by Treese *et al* who studied 84 of 127 patients who had been randomised to intravenous and intracoronary thrombolysis with or without transluminal coronary angioplasty.[19] Group A consisted of 64 patients who showed primary recanalisation of the infarct related vessel with persistent patency at a subsequent follow up angiogram: group B consisted of 20 patients who showed late reopening (n = 5) or a closed infarct related vessel (n = 15) (caused by late reocclusion in nine). There was no difference between the frequency of ventricular extrasystoles in both groups but repetitive ventricular extrasystoles were more common in group A (21 of 64 patients, 32·8%) than in group B (2 of 20 patients, 10%; $p < 0·05$). However, in contrast with the data of Kersschot *et al*,[18] there was no difference in the incidence of inducible ventricular tachycardia.

The results of these preliminary studies indicate that successful early reperfusion may prevent the formation of an arrhythmogenic substrate as shown by the presence of late potentials on high resolution electrocardiography or the results of programmed ventricular stimulation. They[14–16 18 19] raise some important questions:

(*a*) Why does thrombolytic treatment seem to affect the incidence of ventricular late potentials and the results of programmed ventricular stimulation?

(*b*) What is the mechanism for the improvement in prognosis after successful thrombolytic treatment?[20] Is this improvement in prognosis the result of a reduction (albeit small) in infarct size?[21 22] Or are other mechanisms responsible—such as changes in the electrophysiological milieu?

Thrombolytic treatment aims at opening an occluded coronary artery and thus at reducing infarct size, with the ultimate goal of improving prognosis. Reduction in cardiac mortality was shown in various studies of thrombolytic treatment though this was not a consistent finding.[20 23] Outcome was governed by the time from onset of myocardial infarction to thrombolysis, by the patency rate achieved, and possibly by the site of infarction. However, we do not know whether improvement in prognosis after thrombolytic treatment is due to a reduced mortality from heart failure or from arrhythmic causes. In addition, the mechanism underlying an improvement in prognosis has not yet been adequately examined.

The reduction in infarct size achieved by early thrombolysis is relatively small. Ritchie *et al* reported a reduction in infarct size (as a percentage of the left ventricle) from 19% in controls to 15% in patients treated with streptokinase.[21] Bassand *et al* found that the left ventricular ejection fraction was higher (53%) in a group treated with anistreplase than in a group that was not given fibrinolytic treatment (47%).[22] The infarct size was reduced by 31%. In the GISSI trial there was no difference in ejection fraction at the predischarge examination in those assigned to streptokinase and those assigned to standard care.[24] However, patients treated with streptokinase had smaller ventricular volumes and a smaller regional wall motion index than patients given standard treatment. These effects persisted for up to 6 months. Another effect of thrombolytic treatment may be the prevention of aneurysm formation.[25] This beneficial effect was also seen after late thrombolysis (4–10 hours).

It has been suggested that some of the beneficial effects of alteplase such as improved left ventricular function[26] or low mortality[27] may be due to some direct myocardial cellular mechanism that is independent of its ability to lyse intracoronary thrombi.[28–33] The assumption was that alteplase has a direct protective effect on the myocyte or that it dissolves microthrombi.[28] These findings are still controversial. However, they may have major implications for the interpretation of the mechanisms of alteplase.[33]

Current data suggest that a patent infarct related coronary vessel reduces the likelihood of ventricular tachycardia even when infarction of the myocardium is developing. Because studies on thrombolytic treatment were not designed to establish the mechanisms of the observed reduction in total mortality, no definite conclusions can be drawn. This is why studies by Gang *et al*, Eldar *et al*, and Riccio *et al* are of great importance because they suggest a potential mechanism for the improvement in prognosis after successful thrombolytic treatment.[14–16] The correlations between the presence of late potentials and arrhythmic events after myocardial infarction and the low incidence of late potentials in patients with successful early reperfusion suggest that the improvement in prognosis may be due to the prevention of the development of an arrhythmogenic substrate.[6 10]

The factors that govern the genesis of late potentials during the evolution of myocardial infarction are still poorly understood. Gang *et al* suggested several mechanisms that might lead to the absence of late potentials in patients with successful reperfusion (that is those in whom the infarct related artery was open).[14] They postulated that the absence of late potentials may be related to reperfusion because it eliminates ischaemia, allows the return of various plasma constituents to the ischaemic area, permits a rapid washout of the toxic products of anaerobic metabolism, causes contraction-band necrosis, may increase the amount of haemorrhage within the infarct zone, and may cause the generation of oxygen free radicals.[14]

Late potentials originate from small areas within the myocardial infarction in which surviving muscle cells are interspersed with fibrosis. The duration and the degree of local impairment of blood flow govern the extent of necrosis and subsequent fibrosis which may establish an abnormal electrophysiological milieu. Because thrombolysis aims to restore blood flow to the myocardium as fast as possible, early intervention may influence the genesis of an abnormal electrophysiological substrate in different ways. First, blood flow may be reduced for too long to allow recovery of the myocardium; this leads to total necrosis without the survival of any muscle fibres. In this situation no chronic arrhythmogenic substrate should develop. Secondly, incomplete recovery may lead to regional survival of the myocardium after thrombolysis. This may increase the likelihood of a patchy infarct and thus of an "arrhythmogenic substrate". Thirdly, restoration of blood flow may be achieved early enough to allow complete recovery of the myocardium which should prevent the occurrence of an "arrhythmogenic substrate".

Current data suggest that detection of late potentials by high resolution electrocardiography is a way of assessing the likelihood of arrhythmic events after myocardial infarction. Several studies even suggest that it is a more powerful predictor for ventricular instability than long term electrocardiographic recording.[6] High resolution electrocardiography seems to be a powerful tool for identifying the presence of an arrhythmogenic substrate after a patient with acute myocardial infarction has been treated by thrombolysis.[10] Prospective studies using this new technique should help to clarify whether in patients with similar degrees of left ventricular impairment outcome is worse in those with late potentials.

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ORIGINAL ARTICLES

Safety and efficacy of repeat thrombolytic treatment after acute myocardial infarction

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Abstract

Thrombolytic treatment for acute myocardial infarction increases the risk of subsequent reocclusion of the infarct related artery. The efficacy and safety of repeat thrombolytic treatment was assessed in 31 patients treated with streptokinase (n = 13) or tissue plasminogen activator (n = 18) a median of five days (1–716) after the first infusion. The indication for readministration was prolonged chest pain with new ST segment elevation. Efficacy was assessed by infarct artery patency at angiography at a median of eight days after readministration in 22 patients and by non-invasive criteria in 23 patients (reperfusion was deemed to be likely if serum creatine kinase was not increased or reached a peak <12 hours after infarction). Angiography showed patency of 70% of the infarct arteries after readministration of streptokinase and of 75% after tissue plasminogen activator. The corresponding patency rates assessed non-invasively were 73% and 75%. Reinfarction was prevented in nine (29%) patients. Allergic reactions occurred in four of eight patients who received streptokinase twice (plasmacytosis and acute reversible renal failure developed in one patient). Two patients had major bleeding and two minor bleeding, all after tissue plasminogen activator, and one of them died of cerebral haemorrhage.

Repeat thrombolytic treatment results in late patency rates similar to the rates after the initial administration. Allergic reactions were common in those treated twice with streptokinase.

Thrombolysis is now used widely in acute myocardial infarction to reduce mortality[1-4] and to preserve left ventricular function.[5] Thrombolysis of a coronary thrombus, however, results in an infarct related coronary artery with an unstable endothelial lesion and often residual thrombus. Angiographic studies showed a rate of about 20% for early reocclusion after thrombolysis.[6] Reinfarction is associated with further myocardial damage and mortality. Though angioplasty seemed to be an attractive approach to preventing reocclusion, four studies showed no reduction of reinfarction.[7-10] Aspirin treatment has been clearly shown to reduce reinfarction but even so reinfarction occurs in approximately 2% of patients.[2] Another approach is to repeat thrombolytic treatment, either with the same or a different agent, if acute coronary thrombosis recurs.

The benefits of repeat thrombolytic treatment for threatened reinfarction may resemble those of the initial administration, but the risks and benefits have not been well described. We report the results of repeat thrombolytic treatment in 31 patients with threatened reinfarction.

Patients and methods

We studied 31 patients (22 men and nine women, mean (SD) age 58 (9) years) who had all been treated with intravenous thrombolysis for acute myocardial infarction. Indications for initial thrombolysis included ischaemic chest pain lasting more than 30 minutes with onset less than six hours before thrombolytic treatment and associated ST segment elevation of ≥1 mm in two limb leads or V4–V6 or ≥2 mm in leads V1–V3. The initial thrombolytic treatment was an infusion of streptokinase 1·5 million units intravenously over 30 minutes in 23 patients and of recombinant tissue plasminogen activator 100 mg intravenously over three hours in eight patients. In all patients treatment with aspirin (50–300 mg per day) was started on admission to the coronary care unit and 12 patients were also given dipyridamole (400 mg daily). Heparin was given intravenously for at least 48 hours in 19 patients, with dose adjustment to maintain the activated partial thromboplastin time between 90 and 110 seconds. Treatment with oral β blockers was started within three days of admission in patients without contraindications. One patient underwent angioplasty of a severe stenosis of the left anterior descending coronary artery seven days after initial thrombolysis and three days before readministration.

STUDY PROTOCOL

Thrombolysis was repeated in patients in whom recurrent ischaemic pain lasting >30 minutes developed despite nitrate treatment and who fulfilled the criteria for ST segment elevation described above. Patients were given the same dose of either streptokinase or tissue plasminogen activator as was used for the initial treatment. All patients were treated by thrombolysis within six hours of the onset of the second episode of pain. The physician chose the thrombolytic agent; though streptokinase was generally avoided between seven days and three months after initial streptokinase treatment and in patients with allergic reactions to their first dose of streptokinase. Steroids or antihistamines were not routinely administered before repeat streptokinase treatment, but one patient did receive intravenous hydrocortisone before readministration. Concomitant treatment was similar to that during the initial administration; all patients were given aspirin and most were given intravenous heparin.

All patients were observed closely for evidence of allergic reactions or hypotension, and any bleeding was noted. Serum concentrations of creatine kinase were measured at least every four hours for the first 24 hours. Coronary arteriography was performed in survivors unless the coronary anatomy had already been defined. Coronary arteriography and left ventriculography were performed by the Judkins technique. The infarct related artery was identified by correlation of the coronary arteriogram with the electrocardiogram and wall motion abnormalities on biplane left ventriculography. The coronary arteries were viewed in multiple projections. The patency of the infarct related artery was coded according to the TIMI criteria.[11]

The time course of creatine kinase release from the onset of thrombolytic treatment was used as a non-invasive marker of early reperfusion. Patients with either no increase in serum creatine kinase or with an early peak of creatine kinase after thrombolytic treatment (<9 or <12 hours) were considered likely to have achieved reperfusion,[12] though we have no independent validation of the specificity or sensitivity of these indices.

We excluded from the enzyme analysis patients in whom sampling was inadequate for reliable timing of the enzyme peak. We also excluded patients in whom persistence of raised creatine kinase concentrations after the index infarction made it difficult to time a "hump" on the washout curve.

Results

Table 1 shows the baseline characteristics of the study group. The threatened reinfarctions occurred at a median of 5 (range 1–716) days after the initial infarction. Table 2 shows the drug treatment that patients were receiving immediately before threatened reinfarction. All but two patients were taking aspirin and six patients were still receiving intravenous heparin after the initial thrombolytic treatment. The electrocardiographic changes associated with the threatened reinfarction were in the same coronary artery distribution as initial infarction in all but one patient.

The thrombolytic agent chosen for the repeat treatment was streptokinase in 13 patients and tissue plasminogen activator in 18. The mean (SD) delay from the onset of pain to readministration was 107 (63) minutes. Eight patients received streptokinase on both occasions. Table 3 outlines the treatment given to each patient, the delay between initial thrombolytic treatment and readministration, and the results of enzyme analysis and cardiac catheterisation.

Table 1 Baseline characteristics of the study group

Mean (SD) age (yr)	58	(9)
Sex.		
Male	22	(71%)
Female	9	(29%)
Site of initial infarct:		
Anterior	9	(29%)
Inferior	22	(71%)
Initial thrombolytic agent:		
Streptokinase	23	(74%)
Tissue plasminogen activator	8	(26%)
Angina before initial infarct*	19	(61%)
Angina after initial infarct and before threatened reinfarction	18	(58%)
Hypertension	8	(26%)
Smoking	14	(45%)
Diabetes	3	(10%)

*Angina for > 48 hours before initial thrombolytic treatment.

Sampling for creatine kinase was adequate in 23 patients. One patient underwent an emergency operation for stenosis of the left main coronary artery and another underwent "rescue" angioplasty 2·5 hours after repeat thrombolysis. In five patients not enough samples were taken between six and 18 hours after readministration to determine the time of peak creatine kinase, and in one patient (case 9) in whom thrombolysis was repeated two days after the initial treatment, creatine kinase was still increased by the initial infarct.

Cardiac catheterisation was performed in 22 patients at a median of eight (0–63) days after repeat thrombolysis. Four patients had died, in four the coronary anatomy was already known, and in one elderly patient without inducible angina at exercise testing the physician wanted to avoid catheterisation.

EFFICACY

Table 4 summarises the results of non-invasive assessment of reperfusion and the angiographic assessment of infarct artery patency for the four possible combinations of thrombolytic treatment. Streptokinase achieved late angiographic patency in 70% of patients and tissue plasminogen activator achieved it in 75%. In patients previously treated with streptokinase, readministration with either streptokinase or tissue plasminogen activator resulted in similar rates of reperfusion assessed non-invasively or angiographically. In nine (29%) patients no rise in cardiac enzymes ensued, implying prevention of further myocardial necrosis.

Reperfusion assessed non-invasively and patency at late angiography were not always concordant. Both angiographic and enzyme data were available in 18 patients. Three (23%)

Table 2 Drug treatment at time of threatened reinfarction

Drug	*No (%)*	
Aspirin	29	(94)
Dipyridamole	12	(39)
Intravenous heparin	6	(19)
Subcutaneous heparin	3	(10)
β Blockers	18	(58)
Calcium antagonists	5	(16)
Nitrates*	8	(26)

*Regular oral, sublingual or transdermal, or intravenous infusion.

Table 3 Treatment and outcome of individual patients

Patient	*Agent 1*	*Agent 2*	*Age (yr)*	*Sex*	*Interval (days)*	*Antithrombotic treatment*	*Peak CK on readministration (U/l)*	*Hours to peak*	*Angiographic patency of infarct artery*	*Comments*
1	SK	SK	59	M	2	ASP, DP, HEP	No rise	—	Yes	
2	SK	SK	52	F	3	ASP	484	9	Yes	Allergic reaction
3	SK	SK	65	M	3	ASP, DP	No rise	—	Yes	Allergic reaction
4	SK	SK	62	F	5	ASP	873	*	Yes	Allergic reaction
5	SK	SK	43	M	7	ASP, DP	418	24·5	Yes	Allergic reaction
6	SK	SK	49	M	8	ASP, DP	878	21	No	
7	SK	SK	49	M	190	ASP	369	*	No angiogram	
8	SK	SK	71	F	268	—	1856	5	No angiogram	Sudden death 47 days
9	SK	rt-PA	49	M	2	ASP, HEP	—	—	Yes	Enzymes still raised after 1st infarct
10	SK	rt-PA	59	M	2	ASP	974	13	No	
11	SK	rt-PA	71	M	3	ASP, HEP	—	—	No angiogram	Emergency operation
12	SK	rt-PA	55	M	3	ASP	734	24	Yes	
13	SK	rt-PA	56	M	4	ASP	No rise	—	Yes	
14	SK	rt-PA	68	F	5	ASP	No rise	—	No angiogram	
15	SK	rt-PA	47	M	5	ASP	No rise	—	Yes	
16	SK	rt-PA	48	M	5	ASP	846	4·5	Yes	
17	SK	rt-PA	62	F	7	ASP, DP	No rise	—	No angiogram	Died—cerebellar haemorrhage
18	SK	rt-PA	68	M	9	ASP	5679	17·4	Yes	
19	SK	rt-PA	66	F	11	ASP	1019	*	No angiogram	Died—stroke (embolic)
20	SK	rt-PA	73	M	19	ASP, HEP	794	5	No angiogram	
21	SK	rt-PA	47	M	23	ASP, DP	No rise	—	Yes	
22	SK	rt-PA	46	M	34	ASP, DP	644	12	Yes	
23	SK	rt-PA	48	M	716	—	7522	8·2	No	
24	rt-PA	SK	51	M	1	ASP, DP, HEP	948	—	No	Early angioplasty
25	rt-PA	SK	57	F	2	ASP	736	*	Yes	
26	rt-PA	SK	59	M	3	ASP, DP	No rise	—	No	Allergic reaction
27	rt-PA	SK	66	M	9	ASP	495	11·7	Yes	
28	rt-PA	SK	43	M	169	ASP, DP	504	*	No angiogram	Allergic reaction
29	rt-PA	rt-PA	60	F	4	ASP, DP	No rise	—	No	
30	rt-PA	rt-PA	63	M	12	ASP, DP	584	12	Yes	Bleeding venepuncture site
31	rt-PA	rt-PA	72	F	23	ASP, HEP	674	17	No angiogram	Died early—cardiogenic shock

*Inadequate sampling.
SK, streptokinase; rt-PA, recombinant tissue plasminogen activator (alteplase); CK, creatine kinase (normal <300 U/l); ASP, aspirin; DP, dipyridamole; HEP, heparin.

of 13 patients in whom enzyme analysis suggested reperfusion subsequently had an occluded infarct artery, and three of the five patients in whom enzyme analysis did not support early reperfusion subsequently had a patent infarct artery.

ADVERSE REACTIONS

Allergic reactions were seen in four of the eight patients who received streptokinase on two occasions. The interval between the initial and second administrations was three days in two, five days in one, and seven days in another. The four patients who did not have an allergic reaction were retreated on days 2, 8, 190, and 268. Allergic reactions were characterised by transient fever and rigors. No patients suffered bronchospasm, angio-oedema, or anaphylactic shock with readministration of streptokinase. In one patient plasmacytosis and transient renal impairment subsequently developed.[13] No allergic reactions were seen with tissue plasminogen activator.

Transient hypotension and bradycardia were seen during thrombolytic infusion in five patients—two receiving streptokinase and three tissue plasminogen activator. All patients with significant hypotension had a threatened inferior infarction.

All important haemorrhagic complications were associated with treatment with tissue plasminogen activator. A 62 year old woman died after receiving tissue plasminogen activator for threatened reinfarction seven days after initial treatment with streptokinase. Neurological signs developed six hours after the start of treatment and necropsy showed a recent cerebellar haemorrhage. In a second patient a large groin haematoma developed at the site of arterial puncture after angioplasty three days earlier and required transfusion of 1·5 litres of blood. One patient had a single

Table 4 Patency and reperfusion rates after repeat thrombolytic treatment

Agent 1	*Agent 2*	*No*	*Angiographic patency**	*Reperfusion (enzymes)* *No CK rise*	*Peak CK <9 h or no CK rise†*	*Peak CK <12 h or no CK rise†*
SK	SK	8	5/ 6	2/ 6	4/ 6	4/ 6
SK	rt-PA	15	8/10	5/12	8/12	9/12
rt-PA	rt-PA	3	1/ 2	1/ 3	1/ 3	2/ 3
rt-PA	SK	5	2/ 4	1/ 2	1/ 2	2/ 2
Total		31	16/22 (73%)	9/23 (39%)	14/23 (61%)	17/23 (74%)

*Patency = TIMI 2 or 3 flow.
†Time from start of thrombolytic treatment.
SK, streptokinase; rt-PA, recombinant tissue plasminogen activator (alteplase); CK, creatine kinase.

episode of macroscopic haematuria and another experienced prolonged skin bleeding from venepuncture sites.

Three patients died within 30 days of readministration of thrombolytic treatment. One patient died from cerebellar haemorrhage as outlined above, one of an embolic stroke 12 days after readministration, and another of cardiogenic shock 24 hours after readministration. One further patient died suddenly 47 days after threatened reinfarction.

ANGIOPLASTY AND OPERATION

Angioplasty was performed electively within three days of repeat thrombolytic treatment in nine patients. Two further patients had reinfarctions while awaiting intervention; one proceeded to angioplasty and one to urgent coronary surgery. Five other patients subsequently underwent coronary artery surgery. Eleven survivors were initially managed conservatively, but two subsequently required angioplasty for severe angina and one had a late reinfarction.

Discussion

Reinfarction occurs in approximately 9% of patients during the first 12 months after thrombolytic treatment for acute infarction.[14] It is attractive to extrapolate the substantial evidence for benefit seen with initial use of thrombolytic treatment to readministration in the event of subsequent threatened infarction, but the risks and benefits of this approach are not well defined.

Streptokinase is a foreign protein and is antigenic in humans. Possible allergic reactions were reported in 4·4% of patients treated with streptokinase in ISIS–2[2] and 3·4% of patients receiving streptokinase in GISSI–1.[1] Anaphylactic shock occurred in 0·1% of patients treated with streptokinase in GISSI–1[1] and did not occur in ISIS–2.[2] The use of prophylactic steroids is theoretically unlikely to be helpful.[15] In ISIS–2 22% of patients received prophylactic steroids, with no reduction in the reported rate of allergic reaction.

Because most patients already have antibodies to streptokinase from previous streptococcal infections the dose needs to be greater than 1·25 million units to ensure that these antibodies are overcome.[16] Neutralising antibodies sufficient to inhibit conventional doses of streptokinase develop as early as four days after administration. This titre of antibody persists in most patients tested at six months and one year[17] (and D Massell, JB Gill, AGG Turpie, JA Cairns, personal communication). The relation between lytic efficacy and antibody titres is not clear. Moran *et al* found a discrepancy between streptokinase specific IgG measured by a radioimmunoassay technique and the functional streptokinase resistance titre in some patients.[18] Even so, it seems prudent to avoid readministration of streptokinase when antibody titres are likely to be high. The presence of IgE antibodies is likely to increase the risk of immediate allergic reactions, and high IgG titres (in addition to compromising efficacy) may increase the risk of late complications such as serum sickness and Guillain-Barré syndrome, which are occasionally seen after initial treatment.[19–22] It has been suggested that streptokinase resistance titres should be measured before streptokinase is readministered, and the dose increased appropriately.[23] We think that such an approach is untenable because it would delay thrombolytic treatment.

Because anistreplase contains streptokinase a similar incidence of hypersensitivity reactions might be expected. In the German multicentre trial 2·5% of patients receiving anistreplase had allergic reactions[24] and two of 502 patients receiving anistreplase in the AIMS Study suffered anaphylactic reactions.[4] Vasculitis has also been reported after treatment with anistreplase.[25]

Readministration of plasminogen activators such as tissue plasminogen activator and urokinase, which are non-allergenic, is less likely to reduce efficacy and cause allergic reactions. Little is known of the risks of readministration of these agents, however, particularly of haemorrhage during the first few days after initial treatment. These agents are also more expensive than streptokinase.

This study shows that repeat thrombolysis was feasible and was as effective in restoring vessel patency and probably in limiting myocardial necrosis as the initial treatment. Efficacy was assessed by two methods. Patency of a coronary artery late after thrombolytic treatment does not necessarily indicate early patency. We found a similar high frequency of early reperfusion assessed by enzyme analysis and late arteriographic patency, but as expected there were some discrepancies. In nearly a third of patients receiving repeat thrombolytic treatment for prolonged chest pain with ST segment elevation there was no elevation of cardiac enzymes. We believe that reinfarction was prevented in these patients.

Allergic reactions were frequent when streptokinase was given twice, but these reactions were not associated with a lack of lytic efficacy. Transient hypotension was equally common during the initial and repeat infusions and was not confined to streptokinase treatment.

The role of angioplasty and coronary surgery after readministration of thrombolysis is uncertain. Trials of early angioplasty after initial thrombolysis[7–9] and comparison of conservative and invasive management strategies[10 26] suggest that watchful waiting is better than immediate intervention in most patients. These results clearly cannot be extrapolated to patients with threatened reinfarction. We have often offered such patients a revascularisation procedure on the assumption that a patient suffering two acute coronary events is more likely to have a third. There is no firm evidence for this approach and prospective clinical trials are required.

We believe that prompt readministration of thrombolytic treatment is appropriate in patients with threatened reinfarction and is likely to be as safe and effective as the initial treatment. In view of concerns about efficacy and the occurrence of allergic reactions, we think that streptokinase or anistreplase should not be readministered within a year. We need more information on how common high antistreptokinase titres are more than one year after the initial treatment.

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Multivariate analysis in the prediction of death in hospital after acute myocardial infarction

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Abstract

Prognostic factors in patients with acute myocardial infarction based on clinical and investigative data on admission were evaluated prospectively in 111 consecutive patients. Seventeen patients (15·3%) died during hospital stay. Age, a previous infarct, high Killip class, cardiomegaly, high serum concentrations of cardiac enzymes, a low ejection fraction, and a high wall motion score index correlated significantly with in-hospital mortality; whereas sex, risk factors, and pericardial effusion did not. Multivariate analysis showed that age and the wall motion score index were the best predictors of death in hospital. Wall motion detected by cross sectional echocardiography may reflect the extent of myocardial involvement. Age and wall motion score index predicted in-hospital mortality with a sensitivity of 76·5%, a specificity of 91·5%, and a predictive accuracy of 89·2%. Age and the wall motion score index can be determined on admission and are useful for identifying patients at high risk of cardiac death who might benefit from early intervention.

It is clinically useful to identify high risk patients reliably after acute myocardial infarction. Studies showed that clinical assessment to identify high risk patients could be performed within the first day of admission.[1-4] The most powerful predictor of prognosis was the degree of left ventricular pump dysfunction caused by infarction, which the clinical and investigative variables indirectly reflect.[5-7] However, the ambiguity of the clinical findings and the lack of the sensitivity and specificity of these data to assess the function of the left ventricle hamper the prediction of death in hospital in patients with acute myocardial infarction.[1-4]

We attempted to identify the prognostic factors that are associated with outcome (survival or death). To do this we applied a binary logistic regression model to the clinical and investigative data obtained on the first day of admission.

Patients and methods

PATIENTS

From October 1986 to September 1987 we studied 111 consecutive patients with definite acute myocardial infarction—as defined by typical chest pain, electrocardiographic changes, and serial enzyme changes—who were admitted to the coronary care unit of Siriraj Hospital within 48 hours of the onset of chest pain. Seventeen patients (15·3%) died in hospital within 2 weeks of admission.

CLINICAL DATA

We studied 78 men and 33 women (mean age 62·22 (12·60) years (range 33 to 87)). Twenty two patients had a clinical history or electrocardiographic findings of a previous myocardial infarction or both. On admission, 24 (21·6%) patients were in Killip class II, seven (6·3%) patients were class III, and 17 (15·3%) were class IV (table 1).

We noted the following risk factors for coronary heart disease: family history of coronary artery disease, cigarette smoking, hypertension, hyperlipidaemia, diabetes mellitus, alcohol consumption, sedentary work, gout, obesity, contraceptive pills, and personality type (table 2). Cigarette smoking was defined as consumption of $\geq 0·5$ pack/day for ≥ 6 months before the myocardial infarction.[8] Hypertension was diagnosed if the initial value recorded showed a systolic pressure >150 mm Hg or a diastolic pressure >90 mm Hg or if there was a previous history of hypertension with associated treatment.[8] Glucose intolerance was defined as a history of diabetes mellitus or the use of oral hypoglycaemic agents or insulin. Obesity (body-mass index) was defined as the value of equal or more than 30 (weight divided by the square root of height).[8]

INVESTIGATIVE DATA

Table 3 shows data obtained within 24 hours of admission. Q wave myocardial infarction was found in 88 patients (57 anterior and 31 inferior) and non-Q wave myocardial infarction in 23 patients. We examined anteroposterior chest *x* rays of each patient (upright or sitting) taken at a distance of 6 feet for evidence of pulmonary oedema and diversion of blood to

Table 1 Characteristics of survivors and non-survivors of acute myocardial infarction

Characteristic	*Survivors (94)*	*Non-survivors (17)*	*p value*
Age (yr) (SD)	60 84 (12 16)	70 18 (12·51)	< 0·005
Sex			NS
Male	64	11	
Female	27	6	
Old MI	15	7	<0 01
Killip class (SD)	1 6 (1 0)	2·9 (1·1)	<0 005

MI, myocardial infarction.

Table 2 Risk factors in survivors and non-survivors

Risk factors	*Overall No (%)*	*Survivors (94)*	*Non-survivors (17)*	*p value*
Family history	9 (8·1)	9	—	—
Cholesterol*	23 (20·7)	19	4	NS
Triglyceride*	25 (22·5)	21	4	NS
Hypertension	47 (42·3)	38	9	NS
Smoking	69 (62·2)	60	9	NS
Alcohol†	11 (9·9)	10	1	NS
Sedentary work	58 (52·3)	50	8	NS
Gout‡	9 (8·1)	9	—	—
Diabetes mellitus	21 (18·9)	19	2	NS
Obesity	9 (8·1)	8	1	NS
Contraceptive pills§	2/27	2/27	—	—
Personality				NS
Type A	78 (70·3)	67	11	
Type B	33 (29·7)	27	6	

*Cholesterol ⩾ 6·5 mmol/l; triglyceride ⩾ 1·7 mmol/l.
†Regular heavy drinker for > 10 years.
‡Symptomatic hyperuricaemia.
§Treatment for > 5 years.

the upper lobe and to calculate the cardiothoracic ratio. We also noted the increase in cardiac enzymes on the first day of admission.

Cross sectional echocardiography was performed within 24 hours of admission with an Aloka mechanical scanner Model SSD-118 and 3·0 MHz transducer. The images were recorded on 1/2 inch videotape for real time and slow motion playback. We obtained parasternal long and short axis views and apical four chamber and two chamber views. The short axis view was recorded at three levels: mitral (basal), papillary muscle (mid), and apical. A 14 segment model of the left ventricle was used.[5 6 9] The site and severity of the regional myocardial dysfunction were visually evaluated by review of each echocardiographic study and graded by the Herman and Gorlin scoring system for ventricular wall motion[10]: normal = 1, mild or moderate hypokinesia = 2, severe hypokinesia or akinesia = 3, dyskinesia = 4, and aneurysmal = 5. The values determined for each segment were added to give a total score. Thus in patients with normal scores in all 14 segments the wall motion score index was (14 × 1)/14 = 1. Each study was reviewed by two observers who arrived at a wall motion score index by consensus. The ejection fraction (EF) was determined by a modified Quinones' equation[11 12].

$$EF = ((Ded^2 - Des^2)/Ded^2) + ((Des^2/Ded^2)(\Delta L)),$$

where Ded and Des are the internal dimension at end diastole and end systole respectively level with the tip of papillary muscle in the parasternal short axis view and ΔL is the fractional shortening of the long axis. Because the shortening of the long axis contributes only slightly to the global ejection fraction and because this axis is frequently foreshortened by the apical views, we decided to estimate this component of the ejection fraction equation from a subjective assessment of the wall motion at the apex. Thus $\Delta L = 0{\cdot}15$ with normal motion, 0·05 with apical hypokinesia, 0 with akinesia, −0·05 with dyskinesia, and −0·10 with aneurysm.[9 11] We took the mean of at least three values of the ejection fraction in each patient.[6 9] We used echocardiography to detect pericardial effusion.[13]

STATISTICAL ANALYSIS

All continuous variables were analysed by Student's *t* test for unpaired data. Frequency data were tested by the Z test for proportion or the χ^2 test (tables 1–3).

MULTIVARIATE ANALYSIS

We used multifactorial analysis to identify factors that independently predicted the outcome in our study group and we applied a binary logistic regression model to the data.[14–16]

Y denoted survival and Y = 1 death. If $\underset{\sim}{X}$ is a vector of prognostic factors where $\underset{\sim}{X} = (X_1, X_2, \ldots)$ the logistic regression model specifies that the outcome or non-survival probability, P (Y), is related to the prognostic factors $\underset{\sim}{X}$ by the following equation: $P(Y = 1\underset{\sim}{X}) = 1/1 + \exp(-a - b\underset{\sim}{X})$, where a is a constant term in the equation and b is a column vector of regression coefficients corresponding to the numerically coded factors, and $\exp(K) = (2{\cdot}7182)^k$.

The data (nine factors) from 111 patients were fitted to this statistical model. These factors were the patient's age in years (X_1); the wall motion score index of the left ventricle (X_2); ejection fraction in percentage (X_3); concentrations of creatine kinase (X_4), lactic dehydrogenase (X_5), and aspartate aminotransferase (X_6); the cardiothoracic ratio (X_7), Killip class (X_8), and history of old myocardial infarction (X_9). For the first seven factors (X_1–X_7) actual values were used. The Killip class was 0 if the patient was in class I or class II and 1 if

Table 3 Results of investigation data in survivors and non-survivors (mean (SD))

Investigation	*Survivors (94)*	*Non-survivors (17)*	*p value*
Electrocardiogram:			NS
Anterior	47	10	
Inferior	26	5	
Non-Q MI	21	2	
LVH	5	1	
Chest *x* ray:			<0·025
Ratio	0·57 (0·07)	0·62 (0·06)	<0·025
Upper lobe venous diversion	18	6	NS
Pulmonary oedema	5	2	NS
Cardiac enzymes (U/l)			
CK	975·77 (1109·50)	2420·24 (1895·40)	<0·0005
AST	107·33 (118·04)	492·65 (674·82)	<0·025
LDH	483·67 (437·80)	1214·29 (1200·46)	<0·025
Echocardiogram:			
Ejection fraction (%)	45·23 (12·61)	33·24 (13·47)	<0·0005
WMSI	1·69 (0·38)	2·37 (0·38)	<0·0005
Pericardial effusion	14	3	NS

AST, aspartate aminotransferase; CK, creatine kinase; LDH, lactic dehydrogenase; LVH, left ventricular hypertrophy; WMSI, wall motion score index.

Table 4 Maximum likelihood of fit of logistic regression model in 111 patients with acute myocardial infarction

Variable	*Logistic coefficient*	*Standard error*	*Z value*
Age	0·0897	0·0322	2 79 (p = 0 0052)
WMSI	4 4961	1·0516	4·28 (p < 0·0001)
Constant	−16 7414	3 7651	

WMSI, wall motion score index.

the patient was in class III or class IV. The history of old myocardial infarction scored zero if the patient had no history of previous myocardial infarction and one if he/she did. Data were calculated through the program LOGRESS[17] on the IBM PC/XT computer (table 4).

We applied the binary logistic regression model to age and the wall motion score index as the predictive factors to calculate the probability of death P (Y) in each patient. The sensitivity, specificity, positive predictive value, negative predictive value, and predictive accuracy of the model were calculated in a two-by-two table (table 5). A non-survival probability of $\geqslant 0{\cdot}3$ was regarded as predicting death in hospital.

Results

CLINICAL AND INVESTIGATIVE DATA

There were significant correlations between death in hospital and the following variables: age ($p < 0{\cdot}005$); previous myocardial infarction ($p < 0{\cdot}01$); Killip class ($p < 0{\cdot}005$); presence of cardiomegaly on the chest *x* ray ($p < 0{\cdot}025$); serum concentrations of creatine kinase ($p < 0{\cdot}0005$), aspartate transaminase ($p < 0{\cdot}025$), and lactic dehydrogenase ($p < 0{\cdot}025$); ejection fraction ($p < 0{\cdot}0005$); and wall motion score index ($p < 0{\cdot}0005$) (tables 1–3).

MULTIVARIATE ANALYSIS

All the above nine factors were used for multivariate analysis. The maximum likelihood estimate of the coefficient, its standard error, and the corresponding Z value were also calculated. An absolute value of $Z > 2{\cdot}57$ indicates a significant association ($p < 0{\cdot}01$) between the factors and the patient's survival (table 4). Only age and the wall motion score index were significantly associated with outcome ($p < 0{\cdot}01$). The positive sign of the coefficients indicated that the estimated probability of death in hospital rose with age and the wall motion score index. Table 5 shows the sensitivity, specificity, predictive value, and accuracy of age and wall motion score index determined in the binary logistic regression model.

Table 5 Sensitivity, specificity, and predictive accuracy of age and wall motion score index determined by the logistic regression model

	Outcome		
Predicted outcome	*Non-survivors*	*Survivors*	*Total*
Non-survivors	13	8	21
Survivors	4	86	90
Total	17	94	111

Sensitivity = 13/17 (76·5%), specificity = 86/94 (91·5%), positive predictive value = 13/21 (61·9%), negative predictive value = 86/90 (95·56%), predictive accuracy = 99/111 (89 2%).

Discussion

In an earlier study we combined clinical characteristics and investigative data to identify a subgroup of patients with acute myocardial infarction.[5] The variables previously shown to be useful in the risk stratification of patients with acute myocardial infarction include clinical assessment, initial chest *x* ray, electrocardiographic ST segment mapping, peak serum concentration of creatine kinase, and cross sectional echocardiography.[1–6] The most powerful prognostic factor is the degree of left ventricular pump dysfunction caused by infarction, which these variables indirectly reflect.[5–6 18–20]

PROGNOSTIC FACTORS

The following nine variables, measured on the first day of admission within 48 hours of the onset of chest pain, correlated significantly with an increased risk of death in hospital: old age, a previous infarct, high Killip class, cardiomegaly, high concentration of cardiac enzymes (creatine kinase, aspartate aminotransferase, lactic dehydrogenase), low ejection fraction, and high wall motion score index.

MULTIVARIATE ANALYSIS

Multivariate analysis of these nine variables in patients with acute myocardial infarction showed that age and the wall motion score index were the best prognostic factors. Left ventricular function decreases with age, as the incidence of multivessel coronary artery disease increases.[21] In elderly patients with acute myocardial infarction not only was the myocardium more severely damaged but also the amount of myocardium at risk was high because critical multivessel disease of the coronary arteries was more common.[21] Cross sectional echocardiography allows non-invasive determination of both global left ventricular function and segmental wall motion abnormalities. The extent of myocardial involvement was one of the most useful indices for predicting the outcome of myocardial infarction.[5–7 22] Wall motion score index was a useful predictor of death in hospital after acute myocardial infarction (sensitivity 71%, specificity 90%, and predictive accuracy 87%).[23] Combination of age and wall motion score index in the present study increased the predictive power further (sensitivity 76·5%, specificity 91·5%, and predictive accuracy 89·2%).

Multivariate analysis enabled us to identify the two most important prognostic factors in the prediction of death in hospital.

CLINICAL IMPLICATIONS

Both age and the wall motion score index can easily be obtained on the first day of hospital admission. These two variables can be used rapidly to identify high risk patients who will benefit most from thrombolytic treatment, immediate percutaneous transluminal coronary angioplasty, or coronary bypass grafting.[24-26]

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Ischaemic left ventricular failure: evidence of sustained benefit after 18 months' treatment with xamoterol

Else Vigholt-Sørensen, Ole Faergeman

Abstract

The long term effects of treatment with xamoterol in 14 patients aged 44–73 with mild to moderate heart failure as a result of ischaemic heart disease are reported. After 18 months' treatment with xamoterol, patients were assessed in a randomised double blind crossover comparison of xamoterol (200 mg twice a day) and placebo, each given for one month. Compared with placebo, xamoterol significantly increased exercise duration and work done on a bicycle ergometer and reduced the maximum exercise heart rate. Assessment of symptoms and activities at 12 months by visual analogue and Likert scales showed a trend towards the relief of symptoms of breathlessness and tiredness and an improvement in activity. There was an improvement in the clinical signs of heart failure and no haemodynamic deterioration over a 12 month period as assessed by ejection fraction.

The improvement in exercise tolerance, symptoms, and activities was sustained for 18 months without side effects or development of tolerance.

Chronic heart failure affects approximately 4% of the elderly population and is often a result of myocardial infarction.[1] In the Framingham study 39% of the patients with chronic heart failure had coronary artery disease.[2] In patients with ischaemic left ventricular dysfunction treatment with xamoterol (for up to 3 months) had a beneficial effect.[3-5] Xamoterol (Corwin), a partial agonist at the β_1 adrenoceptor, stabilises the response of the heart to sympathetic drive.[6 7]

It has been suggested that treatment with drugs that have stimulant activity at the β adrenoceptor may be beneficial in the short term but does not show sustained benefit because of a reduction in β receptor density.[8]

The aim of this study was to reassess the effect of withdrawal of xamoterol after chronic treatment for 18 months in patients with mild to moderate heart failure.

Patients and methods

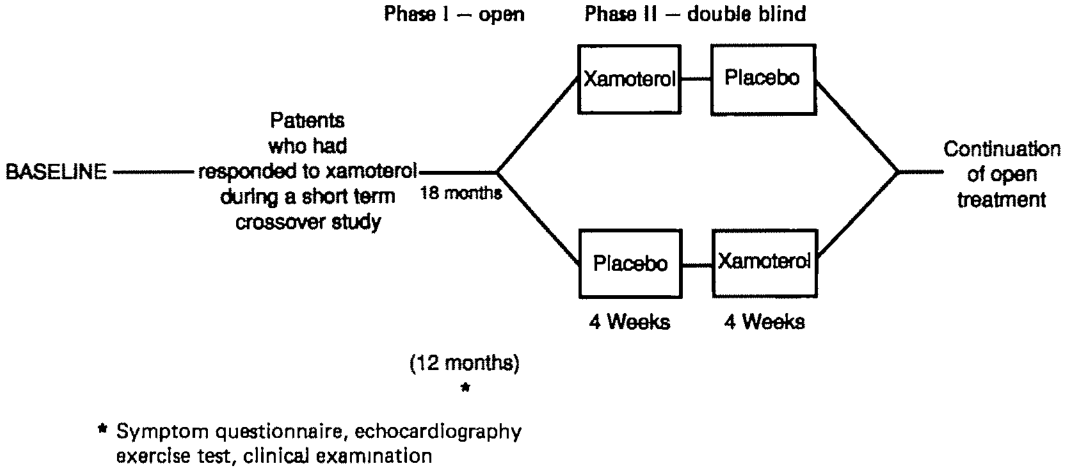
DESIGN

The study had two phases. Phase I was an open study with active treatment (xamoterol 200 mg twice daily) for 18 months. Phase II was a double blind, placebo controlled, crossover study, with treatment periods of 4 weeks (figure). Patients continued treatment in an open study. The protocol was approved by the ethics committee of the Århus Amtssygehus and the study was conducted in accordance with the revised Declaration of Helsinki. Patients gave their verbal consent to inclusion in the study.

PATIENTS

We selected patients aged 44–73 years with symptoms of dyspnoea or fatigue or both on exercise—that is mild to moderate heart failure (New York Heart Association class II–III). They had previously completed a short term placebo controlled study.[9] Patients with severe heart failure (class IV) were excluded.

Other exclusion criteria included: pre-


Phase I — open
Phase II — double blind
BASELINE
Patients who had responded to xamoterol during a short term crossover study
18 months
Xamoterol
Placebo
Placebo
Xamoterol
4 Weeks
4 Weeks
Continuation of open treatment
(12 months)
*
* Symptom questionnaire, echocardiography exercise test, clinical examination

Study design.

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menopausal women; pulmonary disease causing breathlessness on exercise; sinus tachycardia >90 beats per minute; any arrhythmia requiring treatment; aortic or mitral stenosis; hypertrophic obstructive cardiomyopathy; serious non-cardiac diseases; inability to complete 3 minutes of the exercise protocol; concurrent treatment with digitalis, β blockers, vasodilators (hydralazine, prazosin), angiotensin converting enzyme inhibitors, calcium antagonists, and antiarrhythmic agents. Thiazide diuretics at any dose were permitted but daily doses were limited to 80 mg of frusemide, 2 mg of bumetanide, and 100 mg of spironolactone.

METHODS

Clinical examination

Patients were assessed every 3 months during phase I and at the end of each monthly treatment period in phase II. This clinical examination included auscultation of the heart and lungs; measurement of heart rate, blood pressure, jugular venous pulse; and assessment of hepatomegaly and peripheral oedema.

Quality of life assessments

Symptoms and daily activities were assessed at 12 months by Likert and visual analogue scale questionnaires. Each questionnaire included questions on the degree of limitation by breathlessness, tiredness, chest pain, and palpitation. Patients recorded their answers on the visual analogue scale with a vertical mark through a 100 mm horizontal line marked at the two extremes "not at all" and either "very much" or "a great deal". For the Likert scales answers were rated on a 4 or 5 point scale by the physician.[9]

Effort tolerance

Effort tolerance was assessed by a symptom limited exercise test on a Siemens bicycle ergometer that started at 50 W and increased by 25 W every 3 minutes. Heart rate and blood pressure were measured at the end of each 3 minute period, when exercise stopped, and at 1 and 3 minutes after exercise. The duration of exercise was recorded and the total work done calculated. The reasons for stopping exercise were recorded.

Echocardiography

The ejection fraction was measured at baseline and after 12 months by echocardiography. Patients were examined with an Aloka scanner while supine.

STATISTICAL ANALYSIS

Analysis of variance was used to detect any differences between treatments. Any significant treatment effect was assessed by an F test. P values $<0·05$ were regarded as significant. Data generated during the open phase (phase I) were expressed as means and standard error or medians.

Results

CHARACTERISTICS AT BASELINE

After completing a short term placebo controlled study,[9] 18 of the 21 patients who had responded continued in this long term study. Table 1 lists the characteristics of the patients (mean age 62·2 years (range 44–73), 12 men and six women). Seventeen patients were classed in New York Heart Association II and one in class III. The aetiology of the heart failure in this group of patients was ischaemic heart disease. All patients had a history of myocardial infarction.

WITHDRAWALS

Three patients withdrew during phase I. One patient withdrew after 3 months because of deterioration and psychological problems (he later died of a myocardial infarction), one completed 6 months but failed to attend his next appointment, and one patient died after 9 months' treatment because of a lung tumour that had been present before entry to the study. Data from one patient were not included in the analysis because his treatment was not continuous. The analysis therefore includes data from 14 of the 18 patients initially entered in the study. (Since the end of the study two patients have died after 30 and 33 months' treatment. Twelve patients are continuing treatment.)

EXERCISE TEST

Both exercise duration and work done were significantly higher on xamoterol than placebo after treatment for 18 months (table 2). Eleven out of 14 patients exercised for longer on xamoterol; the mean difference in exercise duration was 61·4 seconds ($p < 0·05$). The increase in the amount of work done was 6·3 kJ ($p < 0·05$). The maximum exercise heart rate was significantly reduced from 129·5 (2·3) seconds on placebo to 112·3 (2·3) seconds on xamoterol ($p < 0·0005$). The main reason that patients stopped exercise was dyspnoea, accompanied by fatigue in some patients. Compared with baseline the mean exercise duration after 18 months' treatment was not significantly different. However, after 1 month's treatment with placebo the exercise duration was significantly reduced.

Table 1 Characteristics of patients at baseline

Male, female	12, 6
Age (yr) mean (range)	62·2 (44–73)
NYHA class	
II	17
III	1
Symptoms:	
Dyspnoea	18
Fatigue	9
Angina pectoris	13
Peripheral oedema	5
Medication at entry:	
Diuretic	17
Long-acting nitrates	1
Glyceryl trinitrate	5
Signs of heart failure:	
Basal crepitations	11
Hepatomegaly	1
Raised jugular venous pulse	2
Enlarged heart on chest x ray	7
Past medical history:	
Myocardial infarction	18
Ventricular aneurysm	1
Hypertension	1

Table 2 Exercise results (n = 14)

Variable	*Baseline*	*Xamoterol*	*Placebo*
Exercise duration (s)	419·7 (43·5)	441·1 (15·6)*	379·7 (15·6)*
Work done (kJ)	30·2 (4·7)	31·8 (1·7)†	25·5 (1·7)†
Heart rate at maximum exercise (beats/min)	125·6 (5·2)	112·3 (2·3)‡	129·5 (2·3)‡

p = *0·016; †0·02, ‡0·0002.

Table 4 Median values (mm) for visual analogue scales (for 11 patients)

	Baseline	*After 12 months' xamoterol treatment*
Tiredness	24·0	8·0
Breathlessness	20·0	6·0
Chest pain	4·0	5·0
Palpitation	4·0	4·0

SYMPTOMS AND DAILY ACTIVITIES

Table 3 shows the results with the Likert scales. Those patients who were not troubled by a particular symptom throughout the study have not been included in this analysis. Apart from questions on sleep the answers to every question tended to favour xamoterol, particularly in terms of tiredness, breathlessness, speed and difficulty with walking, and difficulty with daily tasks. Improvement in tiredness and breathlessness was confirmed by assessment with the visual analogue scales (table 4). Patients also reported not having to rest as often while doing daily tasks.

EJECTION FRACTION

The mean ejection fraction at baseline was 43·8 (4·2)% and was not changed after 12 months (43·3 (3·2%)).

CLINICAL SIGNS OF HEART FAILURE

At entry 11 of the 14 patients had one or more signs of heart failure. The most frequent sign of heart failure was basal creptitations (eight patients); after 18 months no patients presented with this sign.

CONCURRENT TREATMENT

All but one patient were receiving diuretics. None of the patients needed an increase in concurrent treatment for heart failure over the 18 month period of the study.

ADVERSE EFFECTS

There were few adverse comments during the study. Most comments related to symptoms of heart failure—that is, dyspnoea, fatigue, pain in the chest, and tiredness. In addition, two patients said they "felt unwell" (in one case a common cold), two patients complained of palpitation, and one patient developed idiopathic hypercalcaemia that reverted to normal within a few months while he was still taking xamoterol.

Discussion

The effect of xamoterol has been established in several studies lasting up to 3 months.[3-5] This study showed that clinical benefit is still maintained after 18 months' treatment with xamoterol.

Table 3 Patients (n) with symptoms and impairment of activities at baseline and after 12 months' treatment

		After 12 months' treatment		
	At baseline (n)	*Better*	*Same*	*Worse*
Tiredness	14	9	4	1
Breathlessness	14	11	3	0
Chest pain	13	7	4	2
Palpitation	10	5	2	3
Difficulty walking	13	9	3	1
Speed of walking	14	13	1	0
Difficulty with daily tasks	13	10	1	2
Speed of doing daily tasks	14	2	11	1
Mood	10	4	5	1
Sleep	8	3	1	4

Over a period of 18 months patients with mild to moderate heart failure would be expected to show signs of deterioration. For example Swerdlow *et al* have shown that as cardiac failure progresses the prognosis worsens.[10] In this present study exercise capacity during 18 months did not change from baseline. However, withdrawal of active treatment followed by 1 month of treatment with placebo significantly reduced exercise duration (by 61·4 seconds—equivalent to 6·3 kJ of work done). These results confirm that efficacy is still demonstrable after 18 months' treatment with xamoterol. After xamoterol was stopped there was no evidence of a sudden deterioration, which suggests there is no rebound effect. In addition to the maintenance of exercise capacity, other measurements indicate that there was no deterioration during the study. The most frequent sign of heart failure at baseline—basal crepitations—was not reported for any patient after 18 months' treatment; no patients needed an increase in concurrent treatment; at 12 months there was no evidence of haemodynamic deterioration as assessed by ejection fraction, and assessment of symptoms and activities at 12 months by visual analogue and Likert scales showed a trend towards a relief of symptoms of breathlessness and tiredness and an improvement in activity.

Apart from xamoterol, long term treatment of heart failure with drugs that have a significant stimulant action on β adrenoceptors has been unsuccessful (for example pirbuterol, prenalterol).[10-12] Only in patients with ischaemic heart disease studied by Glover *et al* were any long term beneficial effects of prenalterol seen—effects attributed to the reduction in exercise heart rate and consequent anti-ischaemic action of prenalterol.[13]

This lack of a sustained effect has been attributed to a drug induced down regulation of β adrenoceptors and a consequent loss of the ability of the above drugs to stimulate the failing heart.[11] Xamoterol is a β_1 adrenoceptor partial agonist that modulates the response of the heart to sympathetic stimulation. In patients with ischaemic heart disease, at low levels of sympathetic activity (during rest and modest exercise) the heart receives modest inotropic support, improving both contraction and relaxation, and during high levels of activity the heart is protected against excessive sympathetic stimulation and the consequent ischaemia. Direct evidence for lack of tachyphylaxis was obtained by Pouleur *et al* who showed that the inotropic effect of xamoterol was maintained after 2 months (200 mg by mouth twice daily).[14] It is probable that the sustained clinical benefit after 3 months'[4] and 18 months' treatment as shown in this study is related to the particular level of partial agonist activity possessed by xamoterol at the β_1 adrenoceptor and its lack of any agonist activity at the β_2 adrenoceptor[6,7]—characteristics that distinguish xamoterol from pirbuterol and prenalterol.

Many patients with heart failure have coexisting angina—72% in this study. Treatment of patients with heart failure and angina poses a dilemma.[15] The aim is to relieve the symptoms of congestion and chest pain and to improve pump function and prevent arrhythmias. Treatment to improve cardiac performance by inotropic stimulation may increase ischaemia and treatment with β adrenoceptor blockers for ischaemia reduces cardiac contractility and therefore increases the risk of pump failure. Xamoterol improved cardiac performance without an increase in myocardial oxygen consumption,[16] had antianginal effects[17] and in this study improved the signs and symptoms of heart failure.

We conclude that xamoterol is an alternative to the conventional treatment of mild to moderate heart failure associated with ischaemic heart disease because it improved exercise tolerance, patient symptoms and activities, and haemodynamic variables and sustained this effect in the long term without side effects or the development of tolerance.

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Transoesophageal echocardiography improves the diagnostic value of cardiac ultrasound in patients with carcinoid heart disease

Lennart Lundin, Johan Landelius, Bertil Andrén, Kjell Öberg

Abstract

Transthoracic and transoesophageal cardiac echocardiography and Doppler investigations were performed in 31 consecutive patients with malignant mid-gut carcinoid tumours. The transoesophageal images allowed measurement of the thickness of the atrioventricular valve leaflets and the superficial wall layers on the cavity side of both atria. The mean thickness of the anterior tricuspid leaflet was significantly greater than that of the mitral valve—a difference not seen in a control group of age-matched patients without carcinoid tumours and with normal cardiac ultrasound findings. In addition, the edges of the tricuspid leaflets were thickened giving them a clubbed appearance. Tricuspid incompetence was detected transoesophageally in 71% of the patients with carcinoid compared with 57% by transthoracic investigation. The inner layer of the right atrial wall in the carcinoid patients was significantly thicker than that of the left atrium and that of both atria in the controls. Furthermore, patients with other signs of severe carcinoid heart disease had significantly thicker mean right atrial luminal wall layer than those with less or no signs of right heart disease.

Transoesophageal cardiac ultrasound investigation improved the diagnosic accuracy and seemed to show the structural changes typical of carcinoid heart disease established by histopathological investigations.

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Malignant mid-gut carcinoid tumours are often associated with a characteristic heart disease with pathognomonic endocardial deposition of myofibromatous tissue.[1-3] In most cases these lesions are confined to the right heart where they are localised in the subendocardium of both cavities and on the tricuspid and pulmonary valves. The cusps are thickened and immobilised resulting in stenosis or incompetence of the valves or both. These features cause pressure and volume overload of the right side of the heart. Restrictive right heart disease has also been described and this is probably the result of the carcinoid related endocardial fibrous thickening of the heart chamber walls.[4 5] In several patients with severe disease similar changes were found in the left heart at necropsy—in some cases associated with cardiac shunts or bronchial carcinoids.[1 6 7]

At present transthoracic echocardiography including imaging and Doppler investigations seems to be the most useful and suitable diagnostic tool for detecting carcinoid heart disease.[8-10] The most commonly described echocardiographic findings are abnormalities of the morphology and motion of the tricuspid and pulmonary valves and an increase in the dimensions of the right heart cavities. In severe cases of right ventricular overload, paradoxical interventricular septal contractions towards the right ventricle have been reported. Doppler ultrasound investigation often detects abnormal valvar blood flow patterns, the most common finding being tricuspid incompetence.

Transoesophageal echocardiography contributes important information to cardiac investigations in aortic and mitral valve disorders.[11] Transoesophageal echocardiography also aids the detection of atrial abnormalities and is a valuable technique for perioperative and intraoperative monitoring of myocardial function.[12 13] The close proximity to the heart facilitates the use of high frequency transducers and reduces common causes of artefacts, both factors that improve the image resolution, especially of the base of the heart.

We examined patients with carcinoid tumours prospectively by both transthoracic and transoesophageal echocardiography to determine whether the transoesophageal approach give additional diagnostic information.

Patients and methods

PATIENTS

Transthoracic and transoesophageal investigations were attempted in 38 consecutive patients with malignant mid-gut carcinoid tumours. Seven patients were excluded from further analyses because of technically inadequate images in five patients and difficulties in advancing the transoesophageal probe and the inability of two patients to tolerate the probe. The remaining group comprised 12 women and 19 men (mean age 58 years (range 41–75)). Two years before one patient had successfully been given tricuspid and pulmonary valve replacements because of severe carcinoid heart disease and right heart failure. The diagnosis of carcinoid disease was histologically confirmed in all patients by the

Grimelius and Masson silver staining techniques and by immunohistochemical examination of tumour tissue obtained at biopsy or operation.[14] Abdominal computed tomography and ultrasound showed liver metastases in all patients and all had the classic signs and symptoms of carcinoid syndrome—that is flush, diarrhoea, and raised urinary excretion of 5-hydroxyindoleacetic acid.

Thirteen patients (eight men and five women, mean age 48 years (range 28–76)) investigated by transoesophageal cardiac ultrasound because cardiac disease was suspected served as a control group for the transoesophageal measurements of valve cusp thickness and atrial wall dimension. In these 13 individuals the findings at transthoracic and transoesophageal echocardiography were regarded as normal.

METHODS

All ultrasound investigations were performed with a Hewlett-Packard real-time scanner (HP Sonos 500, version K). The transthoracic images were almost exclusively obtained with a 2·5 MHz imaging probe (sometimes 3·5 MHz) that also provided facilities for pulsed wave Doppler including colour flow mapping. The methods we used for imaging and measuring are described elsewhere.[10] The tricuspid valve was regarded as abnormal if the leaflets were thickened and cusp motion was reduced. When there was also concomitant pansystolic valvar incompetence (see below) structural abnormalities were actively sought. All patients were examined by pulsed and continuous wave Doppler recordings with spectral analyses and colour flow mapping. A 2·5 MHz imaging transducer was used for the colour flow mapping in all patients because this frequency is more sensitive in adult patients than higher frequencies. Though Doppler ultrasound in several investigations of healthy individuals showed valvar incompetence, especially of the tricuspid valve, there is no definition of what constitutes an abnormal degree of regurgitation detected by Doppler. Recordings showing pansystolic tricuspid valve regurgitation and pandiastolic pulmonary valve regurgitation were regarded as abnormal in this study.

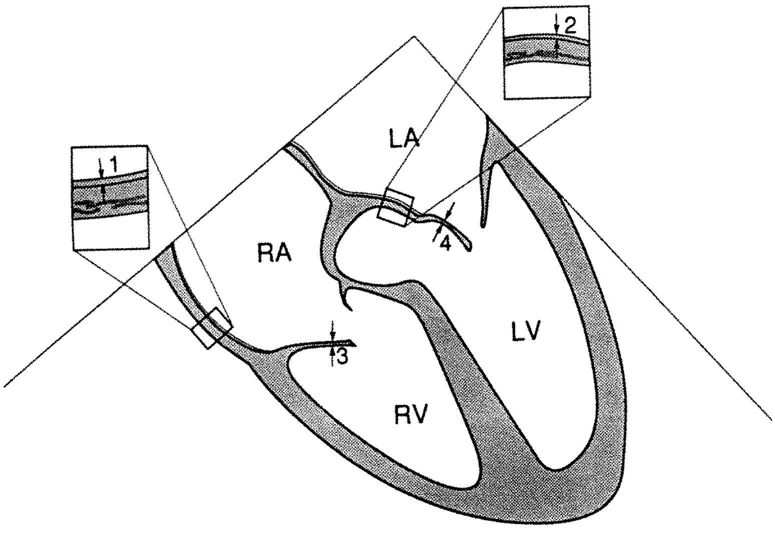

Figure 1 Schematic illustration of the measurements in the transoesophageal images: superficial wall layer on the cavity side of the right (1) and left (2) atrium and thickness of middle part of the anterior leaflet of the tricuspid (3) and mitral (4) valves. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Transoesophageal echocardiography was performed with a Hewlett-Packard echoscope consisting of a 5·0 MHz, 64 element, 11 × 14 mm transducer mounted on the distal tip of a gastroscope. The distal part of the echoscope could be manipulated by two external wheels with a deflection range of 90° left/90° right and 120° up (anterior)/90° down (posterior). Patients fasted for 4 hours before the procedure about which they were fully informed. The echoscope was introduced with the patient in the supine, left lateral position after the echoscope tip had been covered with anaesthetic gel and slight pharyngeal aerosol anaesthesia had been applied. We recorded all registrations on a VHS video recorder using the PAL/Secam standard.

The Hewlett-Packard system displays distance measurements by means of internal callipers on the screen to an accuracy of one hundredth of a mm on images when the closest ranges of the system are used. This numerical accuracy is based on the physical properties of the internal digital matrix of the scanner. Such an accuracy is spurious compared with the capabilities of other components of the imaging system. The best image resolution obtainable is that of the wavelength of the emitted ultrasound at the velocity of speed of 1570 m/s. Thus the resolution would be 0·3 mm in the axial direction of the sector image. But other factors also influence resolution—such as, transducer sensitivity and the engineering physics used to transform the returning analogue reflection pattern for conversion into a digital scan matrix and the different algorithms used to produce the final image presented by a video system. In practical terms, if all measurements on the transoesophageal images are optimised along the axial direction of the image it is reasonable to claim a precision of 0·5 mm because there are no image artefacts and the transducer is close to the heart. Because the technique is used to measure relative differences between pairs of structures the precision of the true physical measurement is less important.

We measured the thickness of the anterior tricuspid and mitral leaflets at their midpoints and the thickness of a layer on the cavity sides of the right and left atrial wall (fig 1). Two experienced investigators independently selected the best available images to measure these dimensions from the video recordings. The results, taken from the system as they were presented, were compared by means of Student's *t* test for paired values. No significant interobserver difference was found. The mean values of the two observers were thereafter corrected to the nearest 0·5 mm.

The data were assessed by Student's *t* test for paired values and independent groups and by analysis of variance with multiple comparisons when appropriate.

P, 25,743

Table 1 Transthoracic Doppler and echocardiographic findings in 31 patients with malignant mid-gut carcinoid tumours

Finding	*No.*	*%*
Tricuspid abnormalities:	19/31	61
Thickened cusp	8/30	26
Decreased cusp motion	6/30	20
Tricuspid incompetence	17/30	57
Pulmonary valve incompetence	9/26	35
Right atrial enlargement	18/31	58
Right ventricular enlargement	10/31	32
Paradoxical septal contractions	8/31	26
Normal right heart	7/31	23

Results

Transthoracic investigation

A right heart abnormality was found in 24 (77%) of the 31 patients. Table 1 shows the frequency of the different abnormalities. Tricuspid abnormalities, including the detection of pansystolic tricuspid incompetence by Doppler, were found in 19 (61%). The tricuspid leaflets were thickened in eight (26%) and in severe cases the edges were clubbed. The image resolution did, however, not permit the thickness of the tricuspid leaflet to be measured. Nine (35%) of the 26 patients in whom Doppler registrations of the pulmonary flow were satisfactory had pandiastolic pulmonary valve incompetence. The right atrium and ventricle were enlarged in 18 (58%) and 10 (32%) respectively, and eight (26%) of the patients had paradoxical interventricular septal contractions.

In seven patients transthoracic echocardiography showed a normal right heart (group 1). In eight it showed morphological or functional abnormalities of the tricuspid valve, enlargement of both the right atrium and ventricle, and paradoxical septal systolic contractions (group 3). The remaining 16 patients (group 2) had one or more but not all the signs of right heart disease seen in the patients in group 3.

Transoesophageal investigation

Transoesophageal images of the four cavities of the heart and the aortic, mitral, and tricuspid valves were adequate in all patients but the pulmonary valve was visualised only in a few.

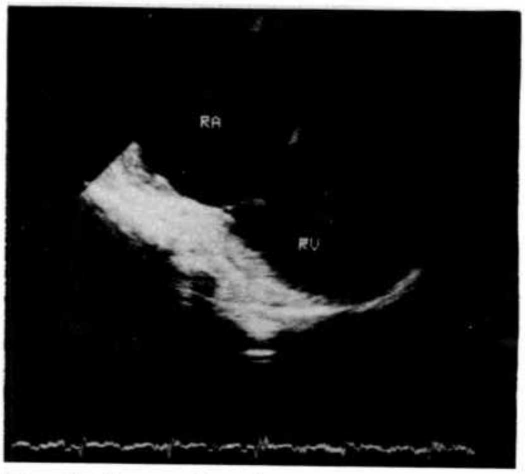

Figure 2 Transoesophageal cross sectional echocardiogram from a patient with carcinoid heart disease showing abnormal anterior tricuspid leaflet with a clubbed edge to the cusp. RA, right atrium; RV, right ventricle.

There were similar difficulties in obtaining adequate colour Doppler registrations of the pulmonary flow; colour flow mapping of the other three valves was good.

In 16 patients (53%) thickening of the edges of the tricuspid leaflets gave them a clubbed appearance (fig 2). Some patients in groups 1 and 2 but none of the controls had clubbed tricuspid leaflets. All patients in group 3 with native valves had thickened leaflets and incompetent tricuspid valves. In one patient who 2 years earlier had tricuspid and pulmonary valve replacements, the bioprosthetic valves were competent and there were no morphological abnormalities. Tricuspid incompetence was seen in two patients in group 1 and 13 in group 2 (table 2). In total, 22 (73%) of the patients with carcinoid had tricuspid incompetence. Tricuspid incompetence was detected by transoesophageal colour flow mapping in five patients in whom transthoracic examinations by pulsed and continuous wave Doppler and colour flow mapping had not shown an incompetent valve.

The mean thickness of the tricuspid leaflet was significantly greater in group 3 than in group 1 ($p < 0·01$), group 2 ($p < 0·05$), or the

Table 2 Transoesophageal ultrasound findings in 31 patients with malignant mid-gut carcinoid tumours grouped by degree of carcinoid heart disease and in 13 controls with normal cardiac ultrasound findings and without carcinoid tumours

	Carcinoid patients				
		Group			
	All (n = 31)	*1 (n = 7)*	*2 (n = 16)*	*3 (n = 8)*	*Controls (n = 13)*
Anterior leaflet thickness (mm) (mean (SD)):					
Tricuspid valve	1·34 (0·30)	1·21 (0·27)**	1·28 (0·31)*	1·56 (0·18)	1·08 (0·19)**
Mitral valve	1·26 (0·25)	1·14 (0·24)	1·28 (0·26)	1·31 (0·26)	1·15 (0·24)
Superficial luminal wall layer thickness (mm) (mean (SD)):					
Right atrium	2·26 (0·56)	2·00 (0·29)***	2·00 (0·26)***	3·0 (0·53)	1·15 (0·24)**
Left atrium	1·21 (0·25)	1·36 (0·24)	1·16 (0·24)	1·19 (0·26)	1·15 (0·24)
Clubbed tricuspid edges (no (%))	16/30 (53)	2/7 (29)	7/16 (44)	7/7 (100)	0
Tricuspid incompetence on Doppler (no (%))	22/30 (73)	2/7 (29)	13/16 (81)	7/7 (100)	0

Asterisks indicate significant differences when group 3 was compared with groups 1, 2, and controls.
*$p < 0·05$; **$p < 0·01$; ***$p < 0·001$.

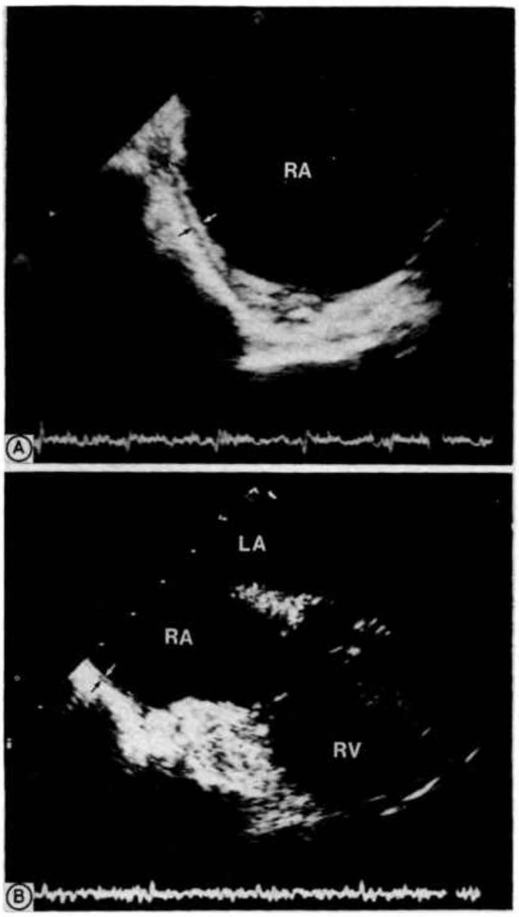

Figure 3 Transoesophageal cross sectional echocardiogram in a patient with carcinoid heart disease (A) and in a patient with normal cardiac ultrasound findings without carcinoid tumour (B). The images show thickening of the superficial wall layer on the cavity side of the right atrium in the patient with carcinoid disease. LA, left atrium; RA, right atrium; RV, right ventricle. The scale is the same in both figures.

control group ($p < 0{\cdot}001$). There were no significant differences in leaflet thickness between the controls and groups 1 and 2 (table 2). Mitral leaflet thickness did not differ significantly between any of the four groups. There was no significant difference between the tricuspid and mitral cusp thickness in any of the groups.

The mean thickness of the normally rather faint wall layer (fig 3B) on the cavity surface of the right atrium was significantly greater ($p < 0{\cdot}001$) than that of the left atrium in the 31 patients with carcinoid; there was no significant difference between these dimensions in the control group (table 2). In addition, in 90% of the patients with carcinoid disease this wall layer was $> +2$ SD thicker than the mean for the control patients. The patients in group 3, who had the most advanced carcinoid heart disease at the transthoracic echocardiographic examination, also had a significantly thicker ($p < 0{\cdot}001$) right atrial wall layer than the patients in groups 1 and 2 or the controls. In addition, the luminal margin of the right atrial wall was often more echodense in patients with carcinoid heart disease, giving the wall a "typical" double contour (fig 3A). In some patients the inner margin of the atrial wall formed crypts and ridges (fig 4). The cardiac abnormalities detected by ultrasound examination were subsequently confirmed at operation when two patients with severe carcinoid heart disease had valve replacement.

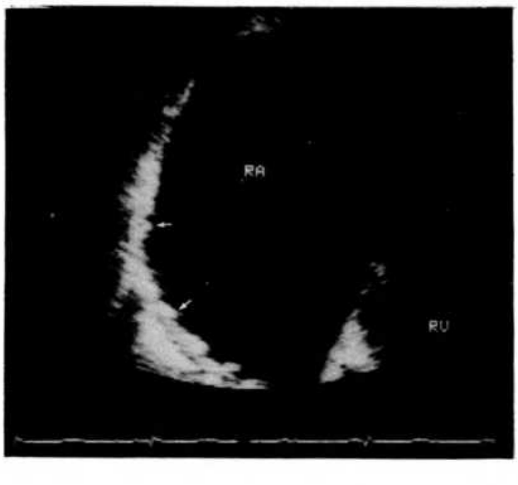

Figure 4 Transoesophageal cross sectional echocardiogram from a patient with carcinoid heart disease showing irregular luminal margin of the right atrial wall (indicated). RA, right atrium; RV, right ventricle.

Discussion

In this prospective study of patients with malignant mid-gut carcinoid tumours, transthoracic cardiac ultrasound investigation detected right heart abnormalities that resembled those reported earlier, although they were somewhat more common in the present study.[1 8–10] The right heart was abnormal in 77% (22/30); the most common abnormalities were morphological or functional changes in the tricuspid valve and enlargement of the right atrium. Pulmonary valve incompetence, right ventricular enlargement, and paradoxical systolic septal contractions were found in 26–35% of the patients.

Transoesophageal cardiac ultrasound gave a closer view of the shape and function of the atrioventricular valve and the characteristics of the atrial walls. We often found that the leaflet margins were clubbed and the cusps of the tricuspid valve were thickened; this accords with histopathological findings in patients with carcinoid disease.[1–3] We found that the middle of the anterior tricuspid leaflet was thicker in patients with severe carcinoid disease than in patients with less severe disease and in the controls. The echocardiographic measurements in carcinoid patients and in the controls were somewhat higher than Sahaskul *et al* found in necropsy specimens of normal hearts.[15] The reason for this discrepancy is not obvious but angular mismatch between the ultrasonic beam direction and the measured structure could result in an overestimation by the ultrasonic measurements. We were, however, careful to choose images obtained with the beam at 90° to the structure. The discrepancy could be the result of the technical difficulties with echocardiographic resolution described in the methods section. However, the limit of resolution is likely to be $<0{\cdot}5$ mm rather than $>0{\cdot}5$ mm. Measurements made with a micrometer might be underestimations because the tissues may have been compressed. Finally, living tissues with normal tissue fluid dynamics may truly have different dimensions after death.

Although the angle between the tricuspid flow and the ultrasound beam often made flow velocity determinations by spectral Doppler analysis impossible, transoesophageal colour flow mapping detected tricuspid incompetence in five patients in whom it was not detected by transthoracic investigations. The pulmonary valve and its flow patterns, however, were more often successfully investigated by transthoracic rather than transoesophageal investigation, although in a few patients the pulmonary valve characteristics were well displayed by transoesophageal echocardiography.

Because the transoesophageal transducer was close to the atria it generated images that showed different types of atrial wall morphology in patients with and without carcinoid heart disease. In controls the walls of both atria had a double contour with a thinner echodense layer of similar thickness on the cavity side. In most patients with carcinoid heart disease this layer was sharper and significantly thicker in the right atrium than in the left atrium and thicker than in both atria in the controls. The abnormalities of the right atrial wall were also more pronounced in patients with other signs of severe carcinoid heart disease. The mean (SD) luminal atrial wall layer which was 2·26 (0·56) mm in the carcinoid patients, could be the echocardiographic image of the carcinoid endocardial myofibromatous tissue deposition, which histology showed was approximately 2 mm thick.[3] At operation in two patients with severe carcinoid heart disease we found patchy irregularities that seemed to increase the endocardial thickness. This may explain why transoesophageal echocardiography showed thickening of the inner layer of the right atrial wall and irregularities of the inner surface of the atrial wall which in some sites may have made the atrial wall trabeculation more pronounced.

We found that transoesophageal echocardiography improved the sensitivity of cardiac ultrasound investigation in patients with carcinoid tumours by showing the subendocardial myofibromatous tissue that is typical of carcinoid heart disease. The increase in tissue dimensions accorded with earlier histological estimations. Transthoracic cardiac ultrasound currently seems to be a suitable method of screening patients with carcinoid disease for cardiac abnormalities. The high resolution images obtained by the transoesophageal technique offer a possibility for detection and follow up of less advanced morphological and functional abnormalities. The place of transoesophageal echocardiography in routine practice, however, remains uncertain except in those patients who are poor subjects for transthoracic echocardiography. In patients with prosthetic valves the technique might detect carcinoid lesions on the prosthetic valves; such lesions have been found at necropsy in one patient.[16]

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Echocardiographic diagnosis of a ruptured aneurysm of the sinus of Valsalva: operation without catheterisation in seven patients

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Abstract

A ruptured aneurysm of the sinus of Valsalva was diagnosed by Doppler, colour, and cross sectional echocardiography in a consecutive series of seven patients. The diagnoses were confirmed at operation without cardiac catheterisation. Examination by pulsed and continuous Doppler echocardiography showed continuous turbulence in six patients with aneurysms rupturing into the right ventricular outflow tract and in the patient with rupture of an aneurysm of the non-coronary sinus into the right atrium. Colour Doppler echocardiography showed turbulent flow across the defects in all seven patients. A ventricular septal defect with aortic regurgitation was detected in one patient and an associated ventricular septal defect in another.

Doppler, colour, and cross sectional echocardiography were useful non-invasive techniques for diagnosing a ruptured aneurysm of the sinus of Valsalva without the need for cardiac catheterisation.

A ruptured aneurysm of a sinus of Valsalva is relatively rare. It occurs as an isolated defect or with other cardiac anomalies.[1-3] The reported incidence in oriental countries is higher than in Western countries.[3-5] Before cross sectional colour Doppler echocardiography became available ruptured aneurysms of the sinus of Valsalva were difficult to diagnose. The auscultatory findings may resemble those in various other diseases such as coronary arteriovenous fistula, persistent ductus arteriosus, aortic regurgitation, or ventricular septal defect associated with aortic regurgitation.

We assessed the feasibility of diagnosing ruptured aneurysms of the sinus of Valsalva in seven patients with cross sectional colour Doppler echocardiography without the use of cardiac catheterisation.

Patients and methods

PATIENTS

Between May 1987 and April 1989, we examined seven oriental patients (five men and two women aged 28–41 (mean (SD)) 35 (5)) with a ruptured aneurysm of a sinus of Valsalva with cross sectional colour Doppler echocardiography. The diagnosis was confirmed at operation without catheterisation. Six of them had ruptured from the right sinus; one had ruptured from the non-coronary sinus. Pulsed and continuous wave Doppler and colour echocardiography were performed in the standard fashion with an Aloca SSD 860 echocardiograph.

The cross sectional echocardiographic criteria for diagnosis of a ruptured aneurysm of a sinus of Valsalva were: (*a*) the root of the aneurysm was above the aortic annulus, (*b*) the aneurysm was saccular, and (*c*) the size of the aorta above the aneurysm was normal. Doppler and colour echocardiographic study showed: (*a*) continuous turbulence detected by pulsed wave Doppler just distal to the area of rupture; (*b*) continuous turbulence at high velocities detected by continuous wave Doppler and; (*c*) colour flow mapping showed mosaic turbulence across the ruptured aneurysm in real time.

Results

CROSS SECTIONAL ECHOCARDIOGRAPHY

According to the criteria of cross sectional echocardiography alone all seven patients had aneurysmal sacs. In six of them aneurysm affected the right sinus of Valsalva. The aneurysms were of different sizes, but they all protruded anteriorly, caudally, and to the left (fig 1). However, rupture of the aneurysm often could not be established by cross sectional echocardiography alone. In the only patient in whom the aneurysm affected the non-coronary sinus of Valsalva (patient 5, table) it protruded into the right atrium (fig 2).

COLOUR DOPPLER ECHOCARDIOGRAPHY

Both pulsed and continuous Doppler echocardiography showed continuous turbulence in the right ventricle in all six patients with rupture into the right ventricular outflow tract (fig 1); in the patient with ruptured aneurysm of the non-coronary sinus the turbulence was detected in the right atrium (fig 2). An associated ventricular septal defect was suspected in two patients (1 and 2) in whom continuous Doppler echocardiography showed high velocity prominent systolic flow at the level of the subpulmonary ventricular septum just below the aneurysm of the right sinus of Valsalva in the parasternal long axis view (fig 1). At operation a subpulmonary ventricular septal defect was seen in these two patients; however, continuous Doppler echocardiography did not detect an associated ventricular

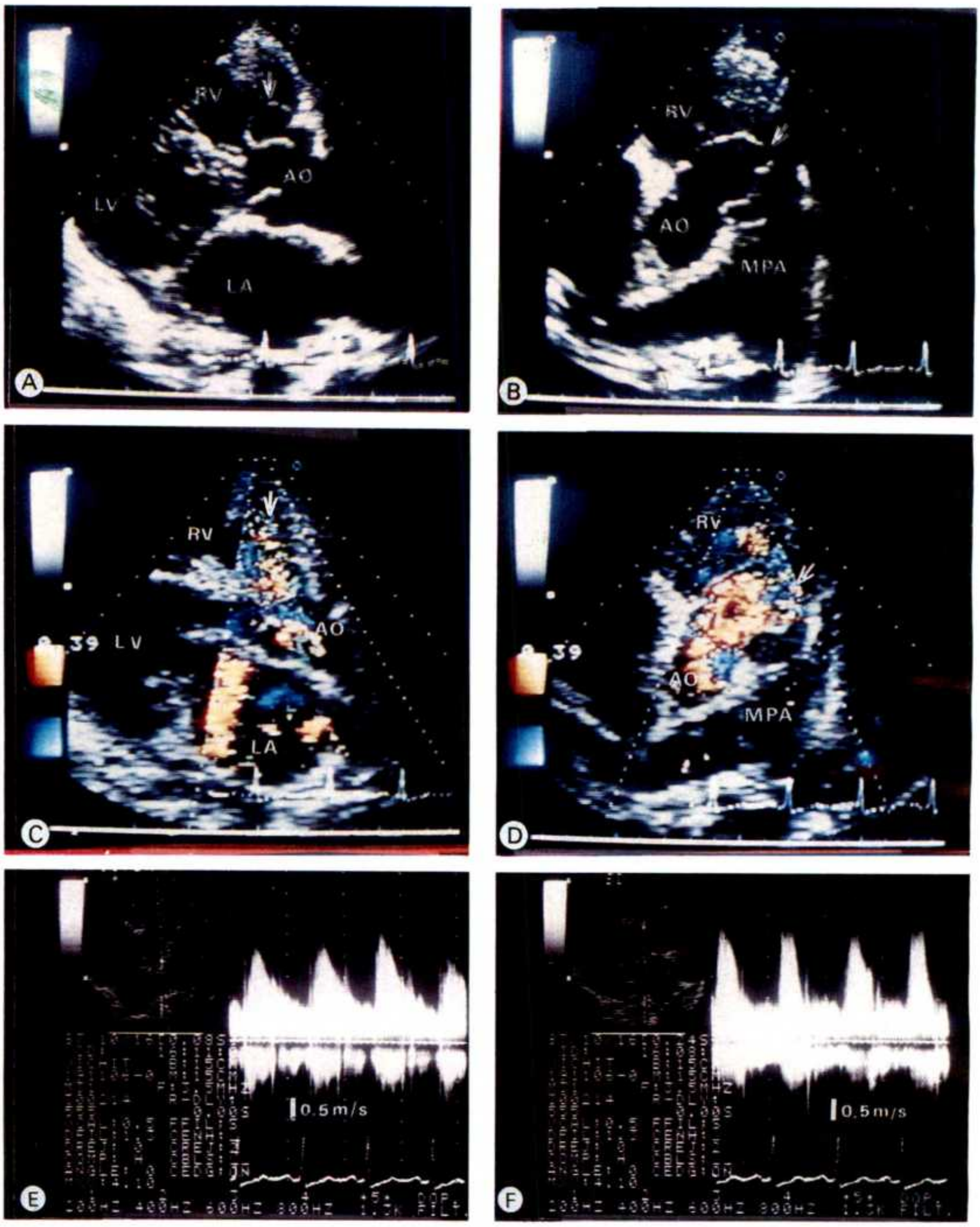

Figure 1 Cross sectional echocardiograms in patient 2. (A) A parasternal long axis view showing an aneurysm of the right sinus of Valsalva (arrow) protruding caudally and located above the aortic annulus. (B) A short axis view at the aortic valve showing the aneurysm (arrow) protruding anteriorly and leftward. Colour echocardiograms in a parasternal long axis view (C) and in a short axis view (D) showing a mosaic turbulent jet (arrow) across the ruptured aneurysm. Continuous wave Doppler echocardiograms showing continuous velocity (E) and prominent high systolic velocity of 2·8 m/s (F) in different views. AO, aorta; LA, left atrium; LV, left ventricle; MPA, main pulmonary artery; RV, right ventricle.

septal defect in another patient (patient 6). Colour flow mapping showed turbulence across the ruptured aneurysm in every patient (figs 1 and 2). Colour Doppler echocardiography showed evidence of associated aortic regurgitation in patient 1; this was confirmed at operation.

Discussion

DOPPLER AND CROSS SECTIONAL ECHOCARDIOGRAPHIC FEATURES OF A RUPTURED ANEURYSM OF THE SINUS OF VALSALVA

Like the patients reported by Chiang *et al*,[5] all six aneurysms of the right sinus protruded anteriorly, caudally, and to the left. This unique protrusion pattern caused blood to flow caudally into the right ventricle across the aneurysm in a parasternal long axis view and anteriorly and leftward in a short axis view (fig 1). Both pulsed and continuous Doppler echocardiography showed continuous high velocity turbulence in the right ventricular outflow tract in all patients with a ruptured aneurysm of the right sinus; in the patient with a ruptured aneurysm of the non-coronary sinus turbulence was detected in the right atrium. The high systolic velocity detected in the subpulmonary region by continuous Doppler echocardiography was strongly suggestive of an associated ventricular septal defect, which was confirmed at operation in two patients. In one patient a ventricular septal defect was not detected by Doppler echocardiography because part of the aneurysm overlay the ventricular septal defect or the jet of ventricular septal defect was not parallel to the echo beam. The surgeon always looked for the associated ventricular septal defect in these patients at operation because such an association is common in oriental countries.[3]

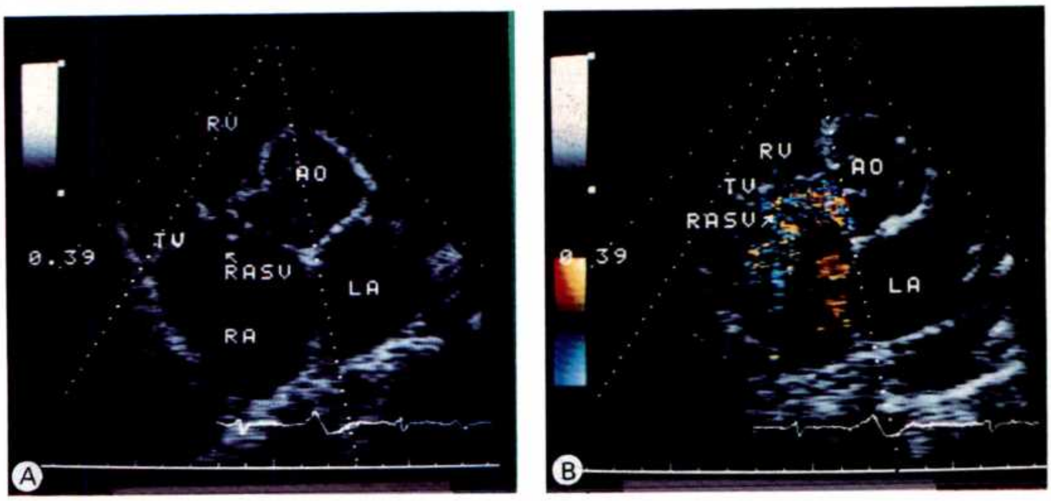

Figure 2 Cross sectional echocardiogram in short axis view (A) in patient 5 showing an aneurysm of the non-coronary sinus of Valsalva (arrow). Colour flow mapping in (B) showed a mosaic turbulent jet (arrow) across the ruptured aneurysm. AO, aorta; LA, left atrium; RA, right atrium; RASV, ruptured aneurysm of the sinus of Valsalva; RV, right ventricle; TV, tricuspid valve.

In all seven patients we detected a continuous turbulent flow by Doppler echocardiography in the chambers with which the ruptured sinus of Valsalva communicated and we saw the mosaic pattern of turbulent colour flow across the ruptured aneurysm. The congenital origin of the disease was confirmed at operation in all seven patients.

In earlier studies contrast echocardiography was useful in aiding diagnosis of a ruptured aneurysm of the sinus of Valsalva.[5,6] We found that the Doppler colour flow technique was probably better than contrast echocardiography in showing the turbulence of blood flow across the site of rupture into the communicating cardiac chamber. We know of no reports of the use of transoesophageal echocardiography in this disorder.[7] In theory transoesophageal echocardiography should be useful for the examination of aneurysms of the sinus of Valsalva, particularly when they have ruptured into left and right atria.

DIFFERENTIAL DIAGNOSIS

A ruptured aneurysm of the sinus of Valsalva must be distinguished from the following conditions: persistent ductus arteriosus, coronary arteriovenous fistula, ventricular septal aneurysm, and ventricular septal defect with aortic regurgitation.[4-6,8,9] Our experience accords with that of Chiang *et al* who found that with right coronary arteriovenous fistula, as with ruptured sinuses, the dilatation lies above the aortic annulus and that the size of the aorta above the dilatation is normal. But, unlike an aneurysm of the sinus of Valsalva, the fistula is usually tubular rather than saccular and often protrudes in a cephalad direction and to the right (following the normal course of the right coronary artery). In contrast, a ruptured aneurysm of the sinus of Valsalva protrudes caudally and to the left. In patients with ruptured aneurysms of the sinus of Valsalva, but not in those with a coronary arteriovenous fistula, pulsed, continuous, and colour Doppler echocardiography will detect continuous turbulent flow at the right ventricular outflow tract. Ventricular aneurysms occur below the aortic annulus, whereas aneurysms of the sinus of Valsalva are always located above the aortic annulus. Doppler echocardiography will not show turbulent flow in the right ventricle in patients with ventricular septal aneurysm without rupture. In patients with a ductus arteriosus flow in the main pulmonary artery is turbulent and there should be no saccular aneurysm at the coronary sinuses. In aortic regurgitation flow in the left ventricular outflow tract is turbulent but only during diastole, whereas rupture of an aneurysm of the right sinus of Valsalva into the right ventricular outflow tract causes turbulence in the tract during both diastole and systole (fig 1). Aortic regurgitation should be sought at echocardiography because it is reported to be more common in patients with ruptured aneurysms of the sinus of Valsalva.[3]

ROLE OF CARDIAC CATHETERISATION

The definitive diagnosis of ruptured aneurysm

Comparison between echocardiographic diagnosis and operative findings in seven patients with ruptured aneurysm of the sinus of Valsalva

			Echocardiography		*Operative findings*	
Case No	*Age (yr)*	*Sex*	*Aneurysm ruptured into:*	*Associated lesions*	*Diagnosis*	*Associated lesions*
1	32	M	RVOT	AR, VSD	Confirmed	Confirmed
2	31	M	RVOT	VSD	Confirmed	Confirmed
3	28	M	RVOT	—	Confirmed	—
4	40	F	RVOT	—	Confirmed	—
5	37	M	RA*	—	Confirmed	—
6	41	F	RVOT	—	Confirmed	VSD
7	35	M	RVOT	—	Confirmed	—

*Non-coronary sinus. AR, aortic regurgitation; RA, right atrium; RVOT, right ventricular outflow tract; VSD, ventricular septal defect.

of the sinus of Valsalva by catheterisation depends not only on the presence of a step up in oxygen saturation in the right heart but also on the demonstration of filling of the right heart chambers by contrast medium from the ascending aorta.[9] At catheterisation we missed a few cases of ruptured aneurysm of the sinus of Valsalva when contrast medium could not be adequately demonstrated in the right ventricle because of the rapid heart rate and high cardiac output in these patients.[9] But turbulent flow can be detected by colour, M mode, and Doppler echocardiography despite rapid heart rate and high output state.[5] We were able to avoid catheterisation before operation in patients with a ruptured aneurysm of the sinus of Valsalva after the condition was diagnosed by cross sectional and colour Doppler echocardiography.

LIMITATION

Combined cross sectional and colour Doppler echocardiography is unlikely to miss a ruptured aneurysm of the sinus of Valsalva. It may be more difficult to be certain whether there is also an associated ventricular septal defect. In an isolated ventricular septal defect the drop-out may not be detected by conventional cross sectional echocardiography alone. But Doppler and colour techniques always detected systolic turbulence in the right ventricle and Doppler showed continuous turbulence when there was a ruptured aneurysm of the sinus of Valsalva. A prominent systolic signal, however, should raise the suspicion of an associated ventricular septal defect. But the absence of such a finding does not exclude a ventricular septal defect.

A ruptured aneurysm of the sinus of Valsalva can be diagnosed precisely by careful non-invasive evaluation with colour Doppler and cross sectional echocardiography. Cardiac catheterisation before surgery can be avoided in these patients.

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EPIDEMIOLOGY

Geographical clustering of risk factors and lifestyle for coronary heart disease in the Scottish Heart Health Study

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Abstract

A large cross sectional study, the Scottish Heart Health Study, of 10 359 men and women from 22 districts of Scotland was undertaken to try to explain the geographical variation of coronary heart disease mortality. Analysis by district showed that of the classic risk factors only cigarette smoking was strongly associated with heart disease mortality among both men and women. Mean diastolic blood pressure was weakly associated with rates among men and high density lipoprotein cholesterol showed a strong negative association among women. Total cholesterol showed a weak negative association with heart disease mortality, but, because the serum concentrations of cholesterol were uniformly high in all districts, a strong association with mortality would not be expected. In both men and women many dietary factors showed moderate or strong associations with mortality from coronary heart disease in a district—of these a low consumption of vitamin C was most notable. Other factors associated with heart disease included alcohol consumption and serum triglycerides among men, and obesity, physical activity, and serum triglycerides among women. Many factors associated with heart disease showed strong intercorrelations. Clustering of risk factors (including smoking, alcohol, and diet among men, and smoking, diet, and obesity among women) was associated with much of the regional variation in heart disease mortality in Scotland.

Regional variation in coronary heart disease mortality has been investigated for many years in the search for clues to the causation of this disease. The early studies were largely of physical factors such as water hardness[1 2] and climate,[3] and used data from the decennial censuses merely to control for socioeconomic variables. However, more recent studies have been interested in the ability of the socioeconomic variables to explain geographical variation.[4-6] There is increasing interest in the association of socioeconomic factors with mortality[7 8] particularly because the social class gradient of coronary heart disease mortality is widening.[9 10]

These studies have been important in providing stimulus and direction to further research. However, they leave unanswered the question of which individual lifestyle features underlie the socioeconomic factors and thus the regional variation. One previous study, which covered all mainland Britain, measured risk factors in individuals to explain regional variation.[11]

We showed that Scotland has a complex and interesting geographical pattern of mortality from coronary heart disease[12] and that a large part of this can be explained by socioeconomic variables,[6] though in contrast with England and Wales water hardness is not important.[13] One of the major aims of the Scottish Heart Health Study was to explain the geographical pattern in terms of individual risk factors.[14] Two papers on the risk factor levels have recently been published.[15 16] This paper reports an analysis of regional data to identify the risk factors associated with coronary heart disease and data on risk factors mediating the association of the socioeconomic variables with heart disease.

Patients and methods

STUDY DESIGN

The study was conducted in local government districts throughout mainland Scotland. Twenty one districts were selected and one, Glasgow City, which was considerably larger than the next largest, was partitioned into two parts, giving twenty two study districts. The selection of districts ensured good geographical spread, a range of urban/rural composition, and coverage of the range of mortality for coronary heart disease.[14]

In each district people were selected by a two-stage cluster sampling design.[17] A random sample of the general practitioners was drawn and their patients sub-sampled to yield a target of 450 people aged 40–59 years consisting of equal numbers of men and women and also equal numbers in the 10 year age groups 40–49 and 50–59. Two of the study districts, Edinburgh and North Glasgow, participated in the overlapping World Health Organisation MONICA study,[18] and included a total of 30

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general practitioners and a target of 800 people in this age range.

MEASUREMENTS

Each person completed an extensive questionnaire that sought information on biographical and economic details, past medical history, standardised respiratory questions, exercise, smoking, diet, alcohol consumption, diet, personality type, and health knowledge. The questionnaire was completed before the individual attended for examination at a local clinic; it was checked for completeness at the clinic. A team of three nurses measured height, weight, blood pressure (the average of two readings with a random zero sphygmomanometer), and carbon monoxide in expired air; an electrocardiogram was also recorded. A sample of venous blood was taken and arrangements were made for a 24 hour urine sample to be collected. Full details of the procedure have been published elsewhere.[14] The fieldwork was carried out between 1984 and 1986.

DEFINITIONS

Hypertension: diastolic blood pressure of at least 100 mm Hg.

Current smoker: self-report of occasional or regular cigarette smoking.

Heavy smoker: self-report of 20 or more cigarettes per day.

Heavy drinker: reported consumption of at least 40 units per week for men and 20 units per week for women (one unit equals a half pint of beer, a measure of spirits, or a glass of wine).

Obesity: body mass index (weight divided by height squared of at least 30·0 kg/m^2 for men and 28·6 kg/m^2 for women).

STATISTICAL ANALYSIS

Correlations between the mean values of each variable for the districts and the district standardised mortality ratios for coronary heart disease were assessed by Spearman's rank correlation coefficient. Given that there were 22 study districts, coefficients larger than 0·425 were significant at the 5% level and those larger than 0·498 were significant at the 1% level. Rank correlation was used to preclude difficulty with variables that were not normally distributed. The variables selected for inclusion in the multiple linear regression analyses were approximately normally distributed.

CORONARY HEART DISEASE MORTALITY

Data on all deaths from coronary heart disease (ICD 410–414, 9th Revision) for the age groups 35–64 years and the period 1979–83 were obtained from the Registrar General (Scotland). We calculated standardised mortality ratios separately for each sex using 5 year age specific mortality rates where the standardised mortality ratio for the whole of Scotland is defined as 100.

Results

One major aim of the Scottish Heart Health Study was to determine the extent to which the major risk factors could explain the geographical variation of coronary heart disease in Scotland. This variation was described in a previous paper.[6] In brief it showed that mortality was in general high in the West and low in the East. Further, in west central Scotland there was a grouping of eight districts with very high mortality that surrounded two other districts with very low mortality from heart disease. This variation is explored in table 1 which shows the rank correlations between standardised mortality ratios for heart disease and serum cholesterol, smoking, and blood pressure separately for men and women. Cigarette smoking stands out as being most strongly associated with heart disease mortality for both men and women. The only other coefficients approaching statistical significance were diastolic pressure in men and high density lipoprotein cholesterol in women (significant at 1%). The latter is a curious result because of the large difference in the size of the coefficients for men and women. Total cholesterol showed a weak negative correlation with heart disease mortality. However, the district mean total cholesterol concentrations were uniformly high for men (range 6·1–6·5 mmol/l) and women (6·3–6·9 mmol/l) and would not be expected to contribute to the regional variation in mortality.

Table 2 shows the relation between the socioeconomic variables obtained from the census that were associated with heart disease and the major risk factors. Two census variables, percentage male unemployment and percentage social classes III–V were selected because they had independent explanatory effects in an earlier study.[6] The importance of these variables was confirmed in the present survey data (table 2) and, as previously, male unemployment is more strongly associated with heart disease mortality. The relation between these social variables and the major risk factors for coronary heart disease also shows interesting results. Among men these social factors are strongly associated with mean diastolic blood pressure and the percentage of

Table 1 Correlation of the major risk factors with mortality from coronary heart disease

	Correlations with heart disease*	
	Male	*Female*
Blood pressure.		
Mean systolic	0·219	0·011
Mean diastolic	0·402	0·234
Percentage with hypertension†	0·223	0·299
Total cholesterol:		
Mean	−0·129	−0·207
Percentage > 6·5 mmol/l	−0·254	−0·116
Mean HDL cholesterol	−0·172	−0·609‡
Cigarette smoking:		
Percentage current smokers	0·655‡	0·834‡
Percentage heavy smokers†	0·574‡	0·758‡

*Spearman's rank correlation coefficients.
†Hypertension and heavy smoking are defined in Patients and methods.
‡Significant at least at the 5% level ($p < 0·05$).

Table 2 Relation between important social variables and coronary heart disease and its risk factors among men and women

	*Percentage unemployed**		*Percentage social class III–V*	
	Male	*Female*	*Male*	*Female*
Coronary heart disease mortality	0·760†	0·775†	0·598†	0·585†
Systolic blood pressure	0·230	0·094	0·524†	0·309
Diastolic blood pressure	0·506†	0·283	0·571†	0·475†
Percentage current smokers	0·783†	0·686†	0·800†	0·816†
Total cholesterol	−0·177	−0·177	−0·114	0·042
High density lipoprotein cholesterol	−0·269	−0·380	−0·388	−0·609†

*Male unemployment rates have been used
†Significant at least at the 5% level ($p < 0{\cdot}05$).

Table 4 Association of other lifestyle features with mortality from coronary heart disease

	Male	*Female*
Alcohol:		
Percentage heavy drinkers	0·519†	−0·358
Median alcohol*	0·446†	−0·269
Obesity:		
Percentage obese	0·171	0·732†
Mean BMI	−0·028	0·624†
Physical activity:		
Percentage strenuous at work	0·355	0·782†
Percentage strenuous at leisure	0·147	0·541†

*Median alcohol consumption was used rather than the mean because the distribution of alcohol values was highly skewed.
†Significant at least at the 5% level ($p < 0{\cdot}05$)
BMI, body mass index.

Table 5 Association of biochemical variables with mortality from coronary heart disease

	Male	*Female*
Urinary creatinine	−0·644*	−0·273
Serum creatinine	−0·500*	−0·047
Serum triglycerides	0·472*	0·600*
Serum uric acid	−0·434*	−0·073
Urinary potassium	−0·556*	−0·705*

*Significant at least at the 5% level ($p < 0{\cdot}05$).

current smokers. Among women only the percentage of current smokers was consistently associated with the social factors, with high density lipoprotein cholesterol and diastolic blood pressure being significantly associated with only one social factor. It is again interesting that total cholesterol shows weak, mainly negative associations with the social factors.

Table 3 shows the association of coronary heart disease mortality with dietary variables. The variables shown are either individual foodstuffs recorded on a food frequency questionnaire or nutrient values estimated from the questionnaire by a method described elsewhere.[19] Several variables show strong associations with heart disease, and, as might be expected, all these variables are themselves highly correlated. These dietary associations are similar for men and women.

In contrast with the similarity seen with diet there were considerable differences between the sexes in the association of heart disease mortality with the other lifestyle features (table 4). Among men there is a moderate positive association with alcohol but for women it is weak and negative. In fact alcohol consumption in women was low with little difference between the districts, so that no association would be expected. Strong positive associations with obesity and strenuous physical activity at work and leisure are only seen among women.

Several biochemical variables showed associations with heart disease mortality (table 5). Of these creatinine, both serum and urinary, showed strong associations only in men. The strong negative association with urinary potassium was found for both sexes. Only weak associations were found for urinary sodium and plasma fibrinogen.

The important questions that the univariate analyses pose are the extent to which the variables are interrelated and to which they have independent explanatory effects for heart disease mortality. The answer to the first is that there is a high degree of interrelation as shown in table 6. For example, among men the percentage of current smokers is strongly associated with percentage unemployment, mean urinary potassium, mean number of eggs, percentage regularly eating lard, and mean vitamin C. Further the pattern of correlation of vitamin C with the other variables is almost identical to that which percentage current smokers has with these variables and the same is true of male unemployment, consumption of eggs, and lard. It seems that there are a set of social, smoking, and dietary factors that are associated with heart disease mortality and which vary in concert between districts. When a multiple regression model is fitted the first of those variables to enter will explain (in a statistical sense) a major part of the effects of the others, though in reality they may have independent effects.

Table 3 Association of dietary variables with mortality from coronary heart disease

	Male	*Female*
Percentage eating:		
No fruit	0·588*	0·537*
No green vegetables	0·491*	0·431*
White bread only	0·611*	0·666*
Lard ≥ twice/week	0·476*	0·638*
Average amount per week:		
Eggs	0·563*	0·573*
Sausages	0·474*	0·572*
Estimated nutritional means:		
Vitamin C	−0·731*	−0·634*
Vegetable fibre	−0·471*	−0·633*
Total fat	0·134	0·382

*Significant at least at the 5% level ($p < 0{\cdot}05$).

Rather than fitting a model with just one of these variables we selected the three variables (percentage unemployed, percentage current smokers, and mean vitamin C) that showed the largest univariate correlations with heart disease mortality. Then three separate models were fitted, each having one of the selected variables forced into the model. The association between the remaining unexplained variation in heart disease and the variables not in the model was assessed from the magnitude of their partial correlations with heart disease mortality. Comparison of the three models identified the variables that show a consistent association with heart disease mortality irrespective of the first independent variable fitted. Thus table 7 shows that for men the percentage of heavy drinkers and mean egg consumption emerge consistently as exerting an independent effect.

Table 6 Correlation matrix of selected variables for men

	Heart disease	*Percentage current smokers*	*Mean diastolic pressure*	*Percentage male un-employment*	*Urinary potassium*	*Percentage heavy drinkers*	*Urinary creatinine*	*Serum creatinine*	*Eggs*	*Lard*
Percentage current smokers	0·655*									
Mean diastolic pressure	0·402	0·431								
Percentage male unemployment	0·760*	0·783*	0·506*							
Urinary potassium	−0·556*	−0·708*	−0·625*	−0·595*						
Percentage heavy drinkers	0·519*	0·467	0·322	0·492	−0·478					
Urinary creatinine	−0·644*	−0·503*	−0·353	−0·507*	0·680*	−0·583*				
Serum creatinine	−0·500*	−0·453	−0·357	−0·356	0·436	−0·617*	0·473			
Eggs	0·563*	0·736*	0·317	0·725*	−0·600*	0·277	−0·568*	−0·355		
Lard	0·476	0·859*	0·337	0·698*	−0·576*	0·219	−0·228	−0·338	0·776*	
Vitamin C	−0·730*	−0·781*	−0·477	−0·774*	0·720*	−0·464	0·527*	0·457	−0·716*	−0·755*

*Significant at the 1% level (p < 0·01).

A similar analysis of the data for women showed a similar pattern in which groups of factors were closely associated (data not shown). Smoking correlated positively with obesity, consumption of lard and white bread, and negatively with urinary potassium and vitamin C. The multiple regression models for women produced much more complicated results than those for men (table 7) with many variables showing an association with heart disease mortality that was independent of the first variable fitted. This complexity is difficult to interpret in detail but it suggests that there may be more than one grouping of lifestyle factors associated with heart disease mortality.

Discussion

This study has found a complex pattern of associations between coronary heart disease mortality and a variety of social, lifestyle, and biochemical variables measured at a regional level. One advantage of this study is that, because it included women as well as men, the results in the two sexes can be compared. Of the classic risk factors only smoking emerges as a strong explanatory variable and its effect is stronger for women than men. A limitation of this study is that the analysis is based on data for groups not individuals. It will only identify factors that explain regional differences and consequently factors that are important at an individual level would not be identified if they varied little between regions. There is, however, a large geographical variation in the mortality from coronary heart disease in Scotland, and the purpose of this paper was to try to explain it.

Table 7 Regression models fitted by selecting a single variable

Variable fitted	*Variables with large* partial correlation coefficients*
Males.	
Unemployment	Percentage heavy drinkers, vitamin C, eggs
Percentage current smokers	Percentage heavy drinkers, urinary creatinine, eggs
Vitamin C	Percentage heavy drinkers, eggs
Females:	
Percentage current smokers	Vigorous work, heavy drinking, urinary potassium, mean systolic, HDL-cholesterol
Percentage unemployed	Percentage current smokers, HDL-cholesterol, vigorous work, lard, triglycerides, heavy drinking, urinary potassium, white bread, serum creatinine, obesity.
Vitamin C	Percentage obese, percentage heavy drinkers, vigorous work, percentage current smokers, urinary potassium, HDL-cholesterol, trigylcerides, percentage unemployment, white bread, sausages, eggs, lard

*Selected as being significant at the 10% level (p < 0·1).
HDL, high density lipoprotein.

The only comparable cross sectional study is the British Regional Heart Study, which investigated men only. It found an association with smoking but it also found a rather stronger effect with systolic blood pressure.[11] The range of systolic pressure among the 24 towns was considerable (from 136 to 153 mm Hg), whereas the range was narrower in the present study (129 to 138 mm Hg). The present study found that only mean diastolic blood pressure among men showed a moderate association with mortality from heart disease. In neither study was there any association between regional values of total cholesterol or high density lipoprotein cholesterol and heart disease mortality in men. Cholesterol concentrations in Scotland are uniformly high[16] and do not contribute to the regional variation. These high values of cholesterol are important in explaining Scotland's position at the top of the world league for heart disease mortality.[20 21] In women too total cholesterol was not associated with coronary heart disease mortality, so that the observation of a strong negative association of high density lipoprotein cholesterol is interesting.

The importance of social factors in the explanation of the geographical variation in mortality from coronary heart disease raises the question of the lifestyle features that underlie this. The difficulty here is that many lifestyle features vary in concert. For example, a diet containing a high content of saturated fat foods (lard, sausages, and eggs) tends also to be one low in fibre, fresh fruit, and green vegetables. Thus all these variables are associated with mortality from coronary heart disease in both men and women. One unexpected finding was the inverse relation between serum creatinine and mortality from heart disease among men. High serum creatinine, through its association with hypertension, might be expected to correlate positively with heart disease mortality. However, the association between serum creatinine and mean diastolic blood pressure was weak, non-significant, and inverse. Further, serum creatine is not just affected by renal function but also by diet.[22] Further, mean serum creatinine shows moderate negative associations with current smoking, unemployment, and the consumption of eggs and lard.

In these circumstances it is difficult and unwise to choose a particular factor and attribute to it the variation in mortality. Thus although vitamin C emerges as the dietary factor most strongly associated with mortality its effects are interlinked with the other dietary factors and with cigarette smoking. The association of alcohol and of egg consumption with mortality in men could in part be due to an association with other factors but in the multiple regression models both exerted consistent independent effects.

The pattern of associations of variables with themselves and with heart disease mortality in women is as complex as that for men. There was considerable overlap with the men in the variables showing a strong association with heart disease mortality; however, some variables (obesity and high density lipoprotein cholesterol) do so only in women. A review of myocardial infarction in women concluded that the classic risk factors for men were also important for women.[23] The review also suggested that high density lipoprotein cholesterol and triglycerides were also of importance but obesity less so. The finding from this study of a grouping of factors of which obesity was a prominent member could suggest that obesity may be more important than previously recognised or that the risk factors among Scottish women may differ from those elsewhere. This could be important in view of the specially high mortality from heart disease among Scottish women.[20]

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CASE REPORTS

Replacement of an aortic valve cusp after neonatal endocarditis

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Abstract

Septic arthritis developed in a neonate after an infection of her hand. Despite medical and surgical treatment endocarditis of her aortic valve developed and the resultant regurgitation required emergency surgery. At operation a new valve cusp was fashioned from preserved calf pericardium. Nine years later she was well and had full exercise tolerance with minimal aortic regurgitation.

Bacterial endocarditis is an uncommon condition in childhood. Despite antibiotics the mortality remains high (8% to 40%)[1-3] and the risk of death is higher in those who need emergency surgery.[4]

Case report

A female infant was born on 29 September 1980 after a normal pregnancy. An emergency caesarean section was performed for fetal distress and the 3·9 kg baby was delivered uneventfully.

When she was 2 weeks old a tender septic spot was noticed on the palm of her left hand and a temperature of 39°C was recorded. Three days later the right hand was swollen and the left thigh became hot and tender. On 26 October she was admitted to her local hospital; an abscess was drained from the left hip joint and treatment with intravenous ampicillin and cloxacillin was started. *Staphylococcus aureus* was cultured from the pus. By 16 November swelling and tenderness of the left thigh developed and osteomyelitis was diagnosed. After additional treatment with intravenous fusidic acid this seemed to settle and she was discharged home on 26 November.

She was again admitted on 9 December 1980 to her local hospital with a history of poor feeding, breathlessness, and weight loss and was transferred two days later to the Children's Hospital, Birmingham for further investigation. On admission she was very ill and in gross cardiac failure. The precordium was hyperdynamic and there were systolic and diastolic murmurs that were loudest in the aortic area. The infection in the hip joint seemed to be quiescent. Echocardiography showed that the non-coronary cusp of the aortic valve was flipping in and out of the left ventricle. The diameter of the aortic root was 1·2 cm on M mode echocardiography. Cardiac catheterisation and angiography showed severe aortic regurgitation through the non-coronary cusp.

That day the aortic valve was explored on cardiopulmonary bypass under hypothermic arrest. The non-coronary cusp of the aortic valve was found to be grossly abnormal. It was rolled up into a small bead and floating freely, attached only by a string to one commissure. The valve cusp was excised and replaced with a piece of preserved calf pericardium (Ionescu-Shiley prosthesis) tailored into the shape of a cusp to extend beyond the centre of the aortic lumen and overlap the other two cusps. Each commissure was extended a little higher than the normal cusps to give proper depth to the oversized prosthetic cusp. During the operation the heart function was seen to improve.

Postoperatively the cardiac failure resolved and she continued to be treated with digoxin and frusemide. The presumed infection was treated with flucloxacillin and fusidic acid. Satisfactory plasma concentrations of the antibiotics were achieved. A further complication was the development of a septic aneurysm of the right common iliac artery, which was repaired surgically one week later. The left hip was also found to be unstable and dislocated. It was splinted in a frog plaster for 4 months and valgus osteotomy was performed in 1986.

At the most recent follow up in August 1989 she was almost nine years old taking part in ballet and with a full exercise tolerance. Clinically there was no evidence of cardiac enlargement. A very soft systolic murmur was heard in the aortic area with a barely audible short early diastolic murmur at the left sternal border. Echocardiography showed normal opening of the aortic valve with slight thickening of the non-coronary cusp. The peak Doppler velocity in the ascending aorta was 1·8 m/s and there was evidence of slight aortic regurgitation. The left ventricular end diastolic diameter was 4·5 cm (slightly greater than the upper limit of normal for a child weighing 21·4 kg). The diameter of the aortic root was 1·8 cm.

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Discussion

This seems to be a unique case of so small a child surviving with a good long term result after reconstructive surgery on the aortic valve after damage by staphylococcal endocarditis. Patients who have infective lesions of the aortic valve often require emergency surgery for life threatening complications. Normally this would be valve replacement. This would have been both undesirable and extremely difficult in such a young child.

Aortic valve repair has been performed previously by extending the cusps with preserved pericardium in adolescents and adults[5] but we have not found a report of cusp replacement in an infant. In our patient the new cusp was carefully fashioned to allow for growth of the child, with the commissures being extended to give proper depth to the oversized cusp. Such prostheses are likely to calcify and this child may require valve replacement later. The good result was probably the result of growth of the native cusps, which in turn gave support to the pericardial cusp. We do not believe that all three cusps could be so successfully replaced. The aortic valve root has grown along with the child. The course so far is extraordinary and promising.

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Hyponatraemia secondary to an inappropriately high release of antidiuretic hormone in cardiac tamponade

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Abstract

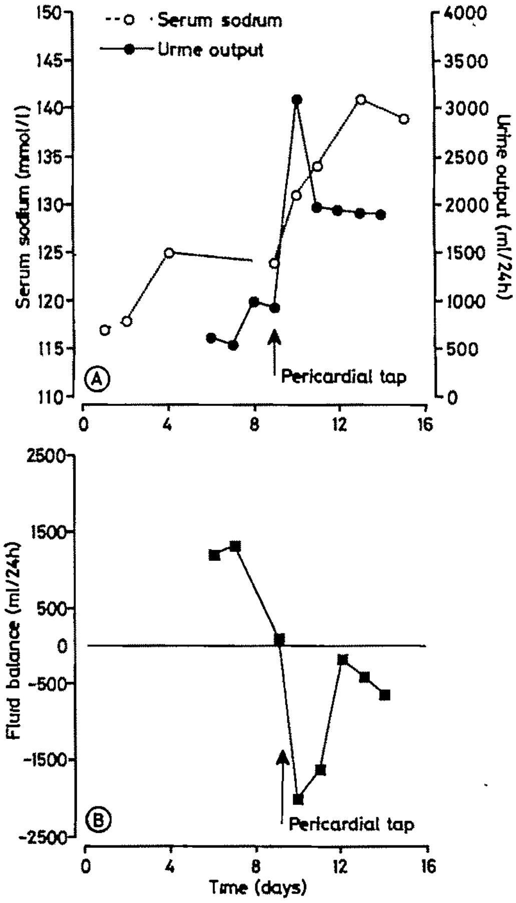
A spontaneous intrapericardial haemorrhage caused cardiac tamponade in a 29 year old paraplegic man who was being treated with warfarin. The associated persistent hyponatraemia, which was believed to be caused by an inappropriately high release of antidiuretic hormone, rapidly resolved after pericardiocentesis.

Release of antidiuretic hormone increases when cardiac tamponade develops.[1] The concentration of serum sodium is usually normal because the balance between fluid and sodium is maintained. We report a case of cardiac tamponade in which excessive fluid retention caused by an inappropriately high release of antidiuretic hormone led to prolonged hyponatraemia.

Case report

A 29 year old man was transferred to the regional cardiothoracic centre from a local spinal rehabilitation unit, to which he had been admitted five months before with traumatic tetraplegia at the level of the sixth cervical vertebrae. The day after his admission to the spinal unit he was treated with warfarin because of symptoms and signs suggestive of pulmonary embolism. Maintenance treatment with warfarin was continued and he also received dantrolene, baclofen, lactulose, and intermittent courses of cephradine and gentamicin for urinary infections. Over three weeks he became progressively more short of breath, but examination on several occasions showed no diagnostic signs referable to his heart or chest. Initial blood tests showed a fall in haemoglobin concentration to 73 g/l and serum sodium to 117 mmol/l and a rise in the serum concentration of aspartate transaminase to 102 IU/l (normal range 12–30). All other tests of electrolytes and liver function were within the normal range.

Though the dose of warfarin was not changed his International Normalised Ratio rose to 10 the day before his transfer; previously it had been well controlled. A chest *x* ray showed considerable cardiomegaly with pulmonary congestion. On admission to the cardiology unit the slightest exertion made him breathless; he did not have a fever, his heart rate was 90 beats per minute, and his blood pressure was 95/70 mm Hg with 10 mm Hg of pulsus paradoxus. Jugular venous pressure was considerably elevated and heart sounds were quiet with no added sounds. An electrocardiogram showed sinus rhythm with low voltage complexes and T wave inversion in the inferior leads. Cross sectional echocardiography confirmed the presence of a large pericardial effusion with diastolic collapse of both the right atrium and right ventricle which with the physical signs confirmed the diagnosis of cardiac tamponade. Treatment with warfarin was stopped and its effects were reversed with fresh frozen plasma and vitamin K. The pericardial effusion was tapped, yielding 1500 ml of heavily bloodstained fluid; a pigtail catheter was left in the pericardial cavity as a drain. The patient had considerable and almost immediate symptomatic relief. A further 500 ml of bloodstained fluid drained over the next 48 hours by which time only a small amount of residual pericardial fluid was detectable by echocardiography. The fluid contained protein (56 g/l); cytology did not show any malignant cells and all



Changes in (A) serum sodium and urine output and (B) fluid balance before and after pericardial tap.

microbiological tests were negative. Immediately after the pericardial fluid was removed the patient had a considerable diuresis and the serum sodium returned to normal within 36 hours without further treatment (figure). At repeat echocardiography one week and four weeks later there was no reaccumulation of pericardial fluid.

Discussion

Hyponatraemia caused by an inappropriately high release of antidiuretic hormone has not previously been reported in cardiac tamponade. The haemodynamic effects of cardiac tamponade acting via arterial and atrial baroreceptors are a potent stimulus to the release of antidiuretic hormone.[1] This response, combined with raised serum concentrations of catecholamines and activation of the renin angiotensin system, is aimed at maintaining arterial blood pressure in the face of a falling cardiac output.[2] The release of atrial natriuretic factor is suppressed (because atrial stretch is reduced[3 4]) and an increase in renal sympathetic outflow increases tubular reabsorption of sodium.[5] The overall physiological response to cardiac tamponade is therefore away from natriuresis and diuresis and the balance of these responses is such that a normal serum sodium is usually maintained. Our patient had prolonged and severe hyponatraemia when progressive cardiac tamponade developed after spontaneous intrapericardial haemorrhage. Apart from a short period of treatment with intravenous fluids in the early stages of this illness, we found no other factor that could have exacerbated or caused the hyponatraemia. Furthermore, the rapid return to normal of serum sodium after pericardiocentesis led us to conclude that the hyponatraemia and cardiac tamponade were directly related. The figure shows that the rise in serum sodium after the removal of the pericardial fluid was paralleled by an increase in urine output. This close relation suggests that the hyponatraemia was caused by intravascular volume expansion and that its rapid resolution resulted from the diuresis that followed pericardial drainage. Though fluid retention would normally be expected in the presence of cardiac tamponade, the extent of the volume changes that led to hyponatraemia in this patient could only be explained by an inappropriately high circulating concentration of antidiuretic hormone.

We do not know why so much antidiuretic hormone was released in this patient. Release of the hormone is controlled not only by local osmotic factors but also by neurogenic stimuli via the vagus and glossopharyngeal nerves, initiated by the effects of changes in systemic haemodynamic function on baroreceptors in the aortic arch and carotid sinus.[6 7] The vagus seems to inhibit secretion of antidiuretic hormone.[8] Alpha and beta sympathetic stimulation have opposing effects on the parasympathetic tone within these pathways and so also contribute to the control of the release of antidiuretic hormone.[7] These nerve pathways, however, were unlikely to have been affected by the spinal injury in this patient so they were probably not part of the underlying pathological mechanism. An alternative hypothesis is that pericardial fluid reduced local afferent vagal tone from the pericardium and so lessened the inhibition of the release of antidiuretic hormone. Induction of cardiac tamponade in anaesthetised dogs was associated with decreased afferent nerve traffic from the pericardium via the right cardiac nerve.[9] This local factor could exaggerate the usual neurogenic stimuli for release of antidiuretic hormone, which are a consequence of the haemodynamic effects of cardiac tamponade.

We conclude that hyponatraemia may develop when there is an imbalance between the antinatriuretic and antidiuretic responses to cardiac tamponade and that it will resolve once the tamponade is relieved.

We thank Dr R J C Hall for his advice, comments, and permission to report this case.

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Aberrant origin of the right coronary artery as a potential cause of sudden death: successful anatomical correction

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Abstract

A man with an aberrant right coronary artery and haemodynamically important prolapse of the mitral valve was successfully resuscitated. The aberrant right coronary artery was thought to be a possible cause of the cardiopulmonary arrest in this patient. Both lesions were corrected at a single operation.

Some believe that the risk of sudden death is higher in patients in whom the right coronary artery arises aberrantly from the left sinus of Valsalva.[1] Many cases of sudden death associated with aberrant left coronary arteries have been reported,[2-4] but sudden death secondary to an anomalous right coronary artery is less well recognised.[5-8] Mitral valve prolapse too predisposes to fatal arrhythmic events.[9-11]

We describe the resuscitation and operative treatment of a patient with an anomalous right coronary artery and mitral valve prolapse.

Case report

A 67 year old man was admitted to hospital after he was resuscitated from a cardiorespiratory arrest that occurred while he was asleep at home.

A heart murmur was detected 16 years before. There was no history of rheumatic fever. In July 1988 mitral valve prolapse and mitral regurgitation secondary to ruptured chordae tendineae were diagnosed after a six month history of exertional dyspnoea and palpitation. In November 1988 fast atrial fibrillation was first noted and the patient was treated with digitalis. Serial electrocardiograms and echocardiograms suggested increasing left ventricular and left atrial dimensions, but the symptoms did not worsen.

During the night of 18 August 1989 the patient's wife (an ex-nurse) was woken by the sound of her husband groaning. She found that he was cyanosed, pulseless, and unresponsive and she started external cardiac massage and mouth to mouth resuscitation. She continued for 20 minutes until an ambulance with a defibrillator arrived. The patient was treated with two DC shocks and with lignocaine and atropine and he regained consciousness. Presumed ventricular fibrillation was converted to fast atrial fibrillation.

When he arrived at hospital he had an irregular pulse of 124 beats per minute. The jugular venous pressure was elevated and the blood pressure was 100/70 mm Hg. The apical cardiac impuse was displaced laterally and there was a grade 4/6 pansystolic murmur at the apex, radiating into the axilla, and an associated thrill between the apex and lower left sternal edge. Auscultation of the chest detected bilateral basal crackles.

The concentration of serum potassium was 3·7 mmol/l and serum digoxin was 0·87 ng/ml. The electrocardiogram confirmed atrial fibrillation with multifocal ventricular extrasystoles, left ventricular hypertrophy, and a strain pattern. The chest *x* ray showed cardiomegaly with an enlarged left atrium and diversion of blood to the upper lobes. Echocardiography showed a dilated left ventricle (end systolic dimension 5·5 cm) with good contraction and a dilated left atrium (5·6 cm). There was prolapse of the posterior leaflet of the mitral valve and ruptured chordae were seen flicking into the left atrium (fig 1A). Doppler echocardiography confirmed considerable mitral regurgitation. Cardiac catheterisation showed a pulmonary artery wedge pressure of 16 mm Hg. Pulmonary artery pressure was 80/30, right ventricular pressure 70/4, and mean right atrial pressure 6 mm Hg. The aortic pressure was 100/70 mm Hg. Left ventricular pressure was 100 with an end diastolic pressure of 16 mm Hg. Cineangiography showed a dilated and hyperkinetic left ventricle with grade IV mitral regurgitation. At coronary angiography the right coronary ostium could not be intubated but aortic root injection suggested that the right coronary artery originated from the left coronary sinus (fig 1B). The origin and course of the left coronary artery were normal. Treatment with diuretics and oral digoxin stabilised the patient's condition.

OPERATION

At operation, performed on 5 September 1989 with cardiopulmonary bypass, the surgeon found an enlarged left atrial cavity, and a typically floppy mitral valve with prolapse of a large segment of the posterior and medial cusps caused by rupture of three major chordae. Elongated chordae caused a partial prolapse of the anterior cusp. Inspection of the coronary ostia from within the aortic root showed that the right coronary artery originated from the left coronary sinus. The right coronary orifice was situated just posterior to the free edge of the intercoronary commissure. The proximal part of the right coronary artery ran in the wall of the aorta to the midpoint of the right coronary sinus. There-

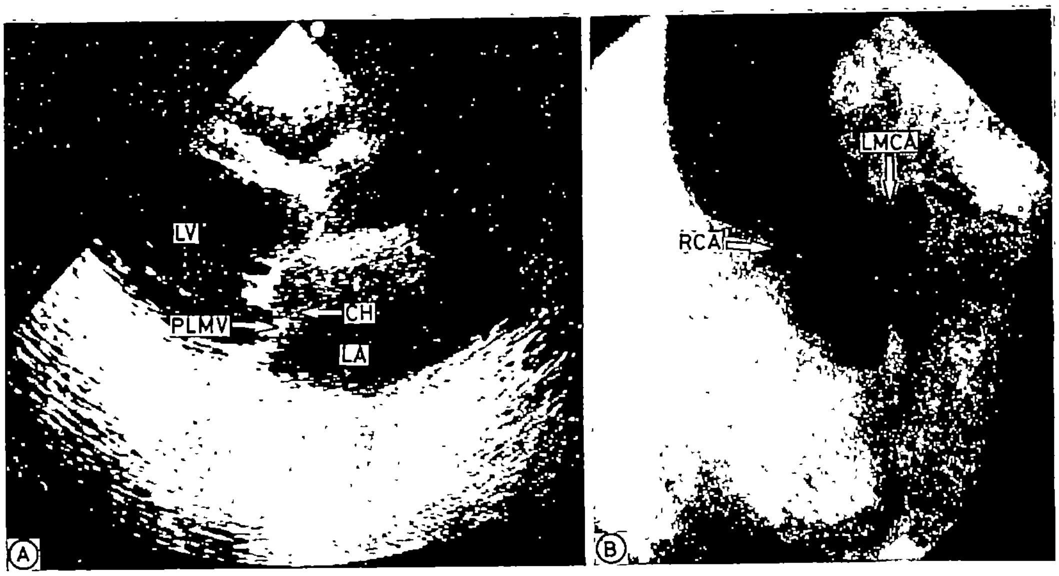

Figure 1 (A) Echocardiogram showing the dilated left atrium and prolapse of the posterior leaflet of the mitral valve. Ruptured chordae were seen flicking into a dilated left atrium. LV, left ventricle; LA, left atrium; PLMV, posterior leaflet of mitral valve, CH, ruptured chordae (B) Aortogram showing normal origin of the left main coronary artery from the left coronary sinus. The right coronary artery originated aberrantly from the left coronary sinus. LMCA, left main coronary artery, RCA, right coronary artery.

after its course was normal (fig 2A). The mitral valve was repaired and the aberrant origin of the right coronary artery was corrected by a technique similar to that used by us to correct an aberrant left coronary artery.[12] The intramural part of the right coronary artery was deroofed (by excising the inner aortic wall) as far as the midpoint of the right coronary sinus. This resulted in prolapse of the intercoronary commissure. The intimal flap of the coronary artery was sutured to the intima of the aorta and the top of the intercoronary commissure was reattached to the aortic wall. This transposed the aberrant coronary artery to its normal position (fig 2B).

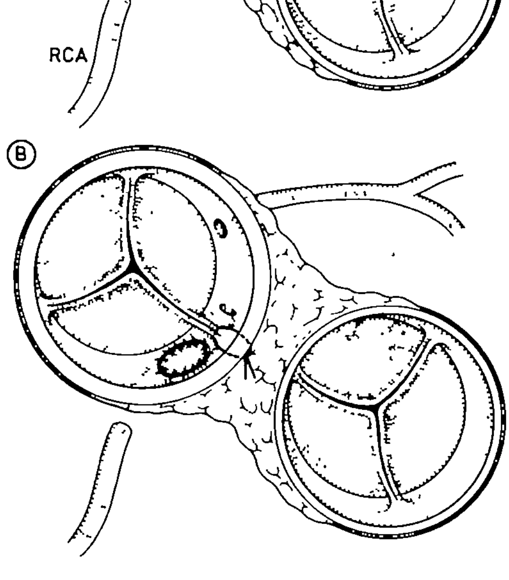

Figure 2 (A) Diagram of the origin of the right coronary artery from the left sinus of Valsalva The right coronary ostium originated from the left sinus just posterior to the intercoronary commissure; it then ran within the wall of the aorta to reach the midpoint of the right sinus before following a normal course. The left coronary artery arises normally and supplies the left anterior descending and circumflex branches. RCA, right coronary artery; LMCA, left main coronary artery; C, circumflex, LAD, left anterior descending; R, right sinus; L, left sinus; N, non-coronary sinus, RV INF, right ventricular infundibulum. (B) Anatomical correction of the aberrant right coronary artery.

The postoperative course was uneventful. The patient remained in sinus rhythm for two days, but subsequently reverted to atrial fibrillation; there was no recurrence of the ventricular extrasystoles seen preoperatively. A postoperative echocardiogram showed a smaller left atrial cavity (3·8 cm).

Discussion

Mitral valve prolapse is associated, albeit rarely, with sudden death. Death is probably caused by arrhythmia.[9 10 13] Kligfield *et al* also reported depressed myocardial function in patients with mitral regurgitation (with or without mitral valve prolapse) who died suddenly.[11] The complexity of arrhythmia in mitral regurgitation seems to be independent of its aetiology.[10] Barlow and Pocock have suggested several mechanisms by which floppy leaflets and elongated chordae could predispose to ventricular extrasystoles.[13] These include endocardial lesions produced by contact between the chordae and left ventricular endocardium, and traction on the papillary muscles by the voluminous leaflets.

Thus sudden death in patients with mitral valve prolapse with considerable mitral regurgitation may be related to the haemodynamic and arrhythmogenic consequences of mitral regurgitation or to mitral valve prolapse itself. Mitral valvoplasty was successful in a patient with mitral valve prolapse and potentially lethal ventricular arrhythmias but without haemodynamically important mitral regurgitation (J B Barlow, personal communication).

Anomalous patterns of origin of the coronary arteries were classified by Vlodaver *et al*.[14] Aberrant origin of the left coronary artery from the right aortic sinus (type II) was shown to be associated with sudden death during exertion. Most reported cases were in young men often with a history suggestive of antecedent episodes of ischaemia, although cardiac arrest can be the first presentation. Patients in whom the proximal left main coronary artery runs between the aorta and the pulmonary artery are at particular risk. Several mechanisms have been suggested for sudden death. These include compression of the proximal left coronary artery between the aorta and pulmonary artery,[4] kinking,[2] and closure of the slit-like orifice of the aberrant left coronary artery by a flap.[3] We believe that during exercise or whenever expansion of the aorta is increased the angle of the left coronary ostium alters, severely stretching the intramural segment and producing luminal narrowing. Furthermore, during diastole when the aortic valve is closed the intercoronary commissure can compress the proximal intramural aberrant artery.[12 15]

Aberrant origin of the right coronary artery from the left sinus of Valsalva of the aorta (type I) was not thought to be a dangerous anomaly—with no reports suggesting an increased risk of sudden death. In 1982, however, a necropsy review of 10 patients with this anomaly showed that three had died suddenly.[6] In 1985 Waller reported the death during exertion of a 17 year old boy with origin of the right coronary artery from the left sinus of Valsalva.[7] Two further cases were reported by Liberthson in 1983[5] and 1989.[8] The latter patient survived an episode of ventricular fibrillation and subsequently underwent successful bypass grafting with an internal mammary artery. Surgical correction and coronary bypass grafting have been described as methods of preventing sudden death in patients with aberrant left coronary arteries.[12 15 16] We suggest that compression of the intramural part of the coronary artery is the major cause of sudden ischaemia when the origin of either the left or the right coronary artery is abnormal.

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TECHNOLOGY

Cardiac catheterisation with 5 French catheters

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Abstract

From the beginning of November 1987 to the end of January 1989, 526 coronary arteriograms and left ventricular angiograms were performed with 5 French coronary catheters. In 448 (85%) patients diagnostic pictures were obtained with three standard types of 5 French catheters (No 4 Judkins): that is, left coronary, right coronary, and pigtail catheters. In 60 patients (11·4%) various other 5 French catheters were required to complete the study. In nine patients (1·7%), a 7 or 8 French catheter was used. Major complications causing cardiac arrest or requiring urgent operation developed in five patients. Sixty two patients (11·77%) had minor complications that required sublingual nitrates or a single bolus of atropine, or developed a haematoma that did not need intervention or had a mild reaction to the contrast material. Complications of moderate severity developed in 17 patients (3·2%): severe chest pain, arrhythmia requiring a temporary pacemaker, contrast reaction associated with hypotension, haematoma requiring blood transfusion, or a transient ischaemic episode. There were no deaths.

5 French catheters were used for routine coronary angiography and left ventriculography in 98·3% of patients. There were no major complications related to femoral artery puncture. The routine use of 5 French coronary catheters should increase the feasibility of safe coronary angiography in outpatients and should reduce the cost of this investigation.

Diagnostic coronary arteriography is recognised as being a safe procedure in experienced hands, with a complication rate of approximately 1%.[1 2] Coronary catheters are generally available in either 7 or 8 French sizes. Improvement in catheter design now allows rapid contrast delivery through 5 French catheters. The chief advantage of using these smaller catheters is that they cause less injury at the site of vascular access. Some operators, however, believe that adequate diagnostic information will not be obtained with 5 French catheters. We report on a large series of diagnostic coronary arteriograms obtained with 5 French catheters in which we found out how often coronary arteriography could be satisfactorily completed with 5 French catheters alone.

Patients and methods

METHODS

We examined the records of cardiac catheterisation in all patients who underwent coronary arteriography from November 1987 to the end of January 1989. We noted all the coronary catheters used to complete the examination, all drugs given during the examination, and any complication that developed in the catheterisation laboratory or in the observation ward where the patients are routinely kept for six hours. During the study period we attempted all examinations with 5 French catheters and used other catheters only if the coronary arteries could not be selectively cannulated or if an adequate image could not be obtained.

A 5 French sheath was inserted into the femoral artery under local anaesthesia and the coronary catheters introduced over a guide wire. We used three standard 5 French catheters: a left coronary catheter (Judkins 4), a right coronary catheter (Judkins 4), and pigtail catheters. The contrast material was Ultravist 370. For left ventricular angiography we injected 30–35 ml of contrast material at 10–15 ml/s. We used biplane angiographic equipment (General Electric CGR) with conventional radiography in all cases. Heparin was not routinely given. All angiograms were performed by consultant cardiologists.

Results

Five hundred and twenty six patients underwent diagnostic coronary arteriography over this 15 month period. Thirty one patients had right and left heart studies. Four patients with suspected severe aortic stenosis were studied by the Sones technique and are not included in this report. All other patients had known or suspected coronary artery disease. Thirty five per cent of patients were studied as outpatients. The mean age of the study group was 55·4 years and 64·4% were men. In five (0·9%) cases the left femoral artery was used because the guide wire could not be advanced from the right side. The right coronary artery was not selectively entered in two patients. Left ventricular angiography was not performed in 17 patients. A satisfactory left ventricular end diastolic pressure recording was obtained in over 95% of patients. Seven of the patients studied had coronary artery bypass grafts.

Table 1 Additional coronary catheters used in 78 patients

Type		No
8 French left coronary catheter	(Judkins 6)	1
8 French left coronary catheter	(Judkins 5)	3
8 French left coronary catheter	(Judkins 4)	2
7 French left coronary catheter	(Judkins 6)	1
7 French left coronary catheter	(Judkins 5)	1
7 French left coronary catheter	(Judkins 4)	1
8 French right coronary catheter	(Judkins 5)	1
8 French right coronary catheter	(Judkins 4)	5
7 French right coronary catheter	(Judkins 4)	3
8 French pigtail catheter		4
7 French pigtail catheter		3
5 French left coronary catheter	(Judkins 5)	36
5 French left coronary catheter	(Judkins 3·5)	4
5 French right coronary catheter	(Judkins 5)	5
5 French right coronary catheter	(Judkins 3·5)	11
5 French internal mammary catheter		18
5 French multipurpose catheter		14
Total		113

In 448 patients (85%) the study was completed with the three standard 5 French catheters. In a further 60 patients (11·4%) the study was completed with a single additional 5 French catheter. Eighteen patients (3·4%) required more than four different coronary catheters to complete the study and in five of these a bypass graft was being studied. In only nine (1·7%) patients were 7 or 8 French catheters required. Coronary artery imaging was satisfactory in 517 (98·2%) patients with a combination of different 5 French catheters. Table 1 outlines the different catheters used in the 78 (14·8%) patients in whom more than the three standard catheters were used.

Table 2 outlines the complications noted during the procedure and up to six hours later. Sixty two patients (11·77%) had minor complications. There were moderately severe complications in 17 patients (3·2%); patients who had a pacemaker inserted for the duration of the procedure were included in this group. No patient required pacing after the procedure was completed. There were major complications in five (0·95%) patients (two patients who required urgent cardioversion went on to immediate coronary artery bypass grafting). There were no deaths in our series. Overall, 22 patients (4·1%) suffered moderate or severe complications. The screening time was recorded in a group of 50 consecutive cases and the mean screening time was 3·01 minutes (range 2·25 to 8·0).

Discussion

The complication rate of coronary arteriography performed as a diagnostic procedure is low.[1] The incidence of major complications reported from two major studies was <1%.[2, 3] Wyman and colleagues reviewed the complication rate of inpatient diagnostic cardiac catheterisations and reported local vascular complications in 4%; 1·6% required operative repair.[4] Some centres are now performing coronary arteriography as a day case procedure and one might expect that earlier mobilisation would increase the risk of local vascular complications. Block *et al* recently published the results of a prospective comparison of outpatient and inpatient cardiac catheterisation with 7 or 8 French coronary catheters.[5] They found a haematoma in 12% of the outpatients compared with 8·5% of the inpatients, a difference that did not achieve statistical significance. In a more recent retrospective review of outpatient cardiac catheterisation with 7 or 8 French catheters local vascular complications were seen in 1·1% of patients up to six hours after the procedure.[6] Cardiac catheterisation with the smaller 5 French catheters should cause less damage of the femoral artery; but there is some concern about the technical aspects of their use[7, 8] and the quality of the radiographic images obtained.

In our experience 5 French catheters are satisfactory in terms of technical manipulation and quality of the radiographic images. In over 500 patients we had to change to 7 or 8 French catheters in only 1·7% of patients. In nearly all of them (98·3%) coronary arteriography and left ventriculography could be completed with a combination of 5 French catheters. We found that in patients with moderately stenosed aortic valves we often needed to cross the valve with a guide wire initially. We did not encounter any particular problems with selective cannulation of the right coronary artery as some have reported.[7] We did, however, occasionally need to change to a multipurpose or internal mammary catheter to cannulate the right coronary artery. Our overall complication rate was low with no deaths and less than 1% of patients developing severe complications.

We found that the frequency of haematoma was low in the first six hours after the

Table 2 Complications (number of patients; (% of total)) occurring during and immediately (<6 h) after cardiac catheterisations

Complications	Mild	Moderate	Severe
Ischaemic	Chest pain or ST segment elevation which resolved with sublingual nitrates, calcium antagonists (40 (7·6%))	Chest pain requiring a nitrate infusion or intravenous morphine (5 (0·9%))	Myocardial infarction or urgent CABG/PTCA (4 (0·7%))
Arrhythmic	Single bolus of atropine (0·6 mg) (18 (3·4%))	Antiarrhythmic agent given or temporary pacemaker (6 (1·1%))	Cardioversion and cardiac arrest (3 (0·57%))
Vascular	Haematoma not requiring transfusion (3 (0·57%))	Transfusion required (2 (0·38%))	Surgical repair (0 (0%))
Allergic	Rash (1 (0·2%))	Hypotension (1 (0·2%))	Anaphylaxis (0 (0%))
Embolic		Transient ischaemic event (3 (0·57%))	Systemic embolus (0 (0%))

CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty.

procedure. We do not have a control group for comparison but the frequency of haematoma was low compared with that reported in other outpatient and inpatient studies.[1 5 9] In Block *et al*'s study bleeding or haematoma formation in the groin were the main reasons that patients scheduled for outpatient cardiac catheterisation were admitted to hospital.[5]

We report our experience when we used primarily 5 French coronary catheters in a large number of patients. Our results suggest that such catheters can be routinely used for diagnostic cardiac catheterisation. By using these catheters we are now examining over 30% of our patients as day-care cases. The routine use of these smaller catheters should result in fewer local vascular complications and this is a great advantage for outpatient cardiac catheterisation.

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MEASUREMENT

Discrepancies in the measurement of isovolumic relaxation time: a study comparing M mode and Doppler echocardiography

C H Lee, F Vancheri, M S Josen, D G Gibson

Abstract

Mitral valve cusp separation on M mode echogram, the mitral valve opening artefact, and the onset of forward transmitral flow recorded by Doppler echocardiography have all been taken to mark the end of isovolumic relaxation, while its onset has been taken either as the aortic closure sound (A_2) recorded phonocardiographically or the aortic closure artefact determined by Doppler technique. Possible differences in the measurement of the isovolumic relaxation time were studied when these landmarks were used in 44 healthy people, 14 patients with mitral stenosis, 21 patients with left ventricular hypertrophy, and 24 patients with dilated cardiomyopathy by recording M mode echograms of the mitral valve, and pulsed and continuous wave Doppler spectra of transmitral flow, with simultaneous electrocardiograms and phonocardiograms. A_2 was effectively synchronous with the aortic artefact. However, when the onset of Doppler flow was regarded as the end of isovolumic relaxation, the interval was significantly longer than when mitral cusp separation on M mode echograms was used: by 25 (10) ms in healthy individuals, by 25 (15) ms in patients with left ventricular hypertrophy, and by 50 (35) ms in patients with dilated cardiomyopathy. In patients with mitral stenosis the interval was only 5 (5) ms longer. The mitral valve opening artefact consistently followed the onset of flow and corresponded much more closely to the E point on the M mode echogram. This shows that it occurred during the rapid filling period and well beyond isovolumic relaxation by any definition.

Thus isovolumic relaxation time measured from A_2 to the onset of transmitral flow or the mitral valve opening artefact differs from that derived from A_2 to mitral valve cusp separation. These intervals cannot be used interchangeably to measure "isovolumic relaxation time".

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Isovolumic relaxation is an important phase of the cardiac cycle. Its length has been used to assess left ventricular diastolic function,[1] to distinguish myocardial restriction from constriction,[2] and to assess the cardiac effects of pharmacological interventions.[3] In his classic text Wiggers wrote of this interval (initially termed isometric relaxation): "Following the closure of the semilunar valves, and until the A-V valves have opened, the ventricle relaxes without any flow of blood either from or into its cavity. This phase may be designated as the isometric relaxation phase".[4] Isovolumic relaxation time has been measured on simultaneous M mode and phonocardiogram recordings as the interval from aortic valve closure (A_2) to the point of mitral cusp separation. More recently, the determination of isovolumic relaxation time has formed part of the Doppler evaluation of left ventricular diastolic function where it has been taken variously as the interval from A_2 to the onset of transmitral flow, A_2 to the mitral valve opening artefact on pulsed wave Doppler recordings, or the aortic valve closure artefact to the onset of transmitral flow recorded by continuous wave Doppler.[5] It has been implicitly assumed that all these measurements are equivalent. Mitral cusp separation is a complex phenomenon, however, and is influenced by many factors apart from transmitral flow, so these different measurements need not necessarily be identical. We therefore explored this possibility, aiming not only to resolve possible confusion but also to use these interrelations to shed light on early diastolic events in normal and abnormal hearts.

Patients and methods

STUDY POPULATION

We studied 44 healthy individuals (27 men, 17 women; aged 18–60), 14 patients with mitral stenosis (three men, 11 women; aged 16–75), 21 patients with left ventricular hypertrophy (11 aortic valve disease, five hypertrophic cardiomyopathy, five hypertensive; 11 men, 10 women; aged 23–75), and 24 patients with dilated cardiomyopathy (16 male, 8 female; aged 12–77, 22 of whom had functional mitral regurgitation). All the patients were in sinus rhythm except for 11 patients with mitral stenosis. There were no significant differences in age among the groups studied.

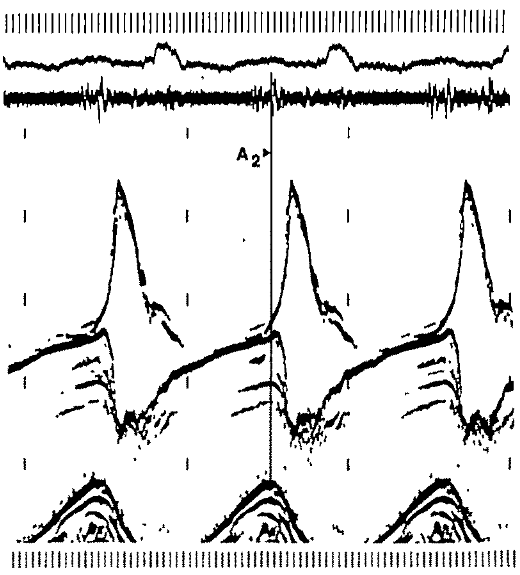

Figure 1 M mode echogram and phonocardiogram from a patient with dilated cardiomyopathy. Isovolumic relaxation time, measured as the interval from A_2 to mitral valve opening, is zero. The second heart sound is reversed in this patient because of left bundle branch block.

M MODE ECHOCARDIOGRAPHY

We recorded M mode echocardiograms of the mitral valve with a 3·0 MHz transducer and ATL Imager Mk300I equipment in the parasternal long axis view with the patients lying in the left lateral position. The minimum gain setting was used to show both the anterior and posterior mitral cusps. We regarded the point of cusp separation as the time of mitral valve opening; cusp separation was clearly defined on all records (fig 1). We did not use D or D′ points because they were poorly defined and thus unreproducible. The E point of the mitral echogram was taken as the point of maximum anterior cusp motion in early diastole. Phonocardiograms and electrocardiograms were recorded simultaneously with a Honeywell recorder at a paper speed of 10 cm/s.

DOPPLER ECHOCARDIOGRAPHY

Doppler recordings were made with Doptek equipment and a 2·25 MHz transducer. Forward transmitral flow was recorded in all patients. Peak mitral flow velocity was initially identified by continuous wave Doppler and then recorded with the pulsed mode and a 3 mm gate. A wall filter of 250 Hz was used in all cases. During the recordings we used the minimum gain setting that gave a complete envelope. The onset of transmitral flow was taken as the time at which the signal rose above the wall filter and was routinely distinguished from the valve artefact, which was recorded separately. Functional mitral regurgitation was carefully sought in all patients by continuous wave Doppler echocardiography. Simultaneous phonocardiograms and electrocardiograms were again recorded at a paper speed of 10 cm/s. We used continuous wave Doppler echocardiography directed towards the left ventricular outflow tract to obtain recordings showing both the aortic valve closure artefact and the transmitral flow.

MEASUREMENTS

Aortic valve closure (A_2) was taken as the onset of the first high frequency component of the second sound recorded on the phonocardiogram, which was routinely checked against the closure point on the aortic echogram. The following measurements were made on the M mode recordings (fig 1): (*a*) The interval from A_2 to mitral cusp separation; (*b*) the interval from A_2 to the E point; (*c*) the interval from minimum left ventricular dimension to mitral cusp separation—when this was >30 ms it was regarded as indicating incoordinate relaxation.[6] We measured the following intervals on the pulsed wave Doppler recordings (figs 2A and B): (*a*) from A_2 to the onset of transmitral flow; (*b*) from A_2 to the leading edge of mitral valve opening artefact; and (*c*) from A_2 to the peak transmitral flow velocity. The interval from the leading edge of the aortic valve closure artefact to the onset of transmitral flow was measured on the continuous wave Doppler recordings (fig 3). We took the mean of measurements made on three cardiac cycles.

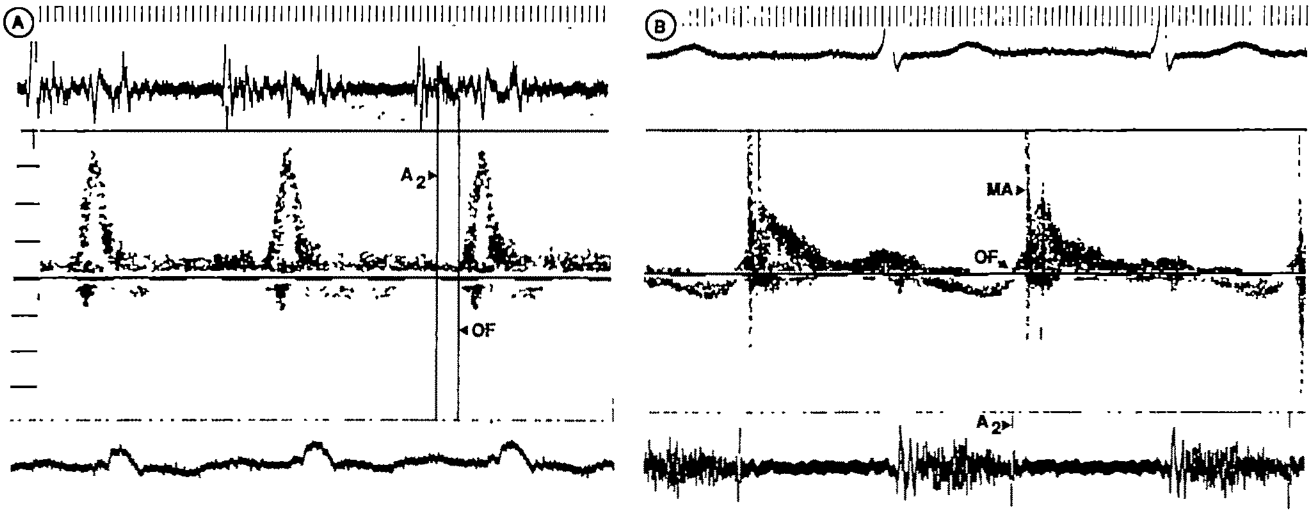

Figure 2 (A) Pulsed Doppler echocardiogram from the same patient as figure 1 showing an interval of 40 ms from A_2 to the onset of forward transmitral flow (OF). Full scale deflection = 4 kHz. (B) Pulsed Doppler echocardiogram showing the relation between A_2, the onset of forward transmitral flow (OF), and the mitral valve opening artefact (MA). Note that the mitral valve opening artefact consistently follows the onset of flow. Full scale deflection = 8 kHz.

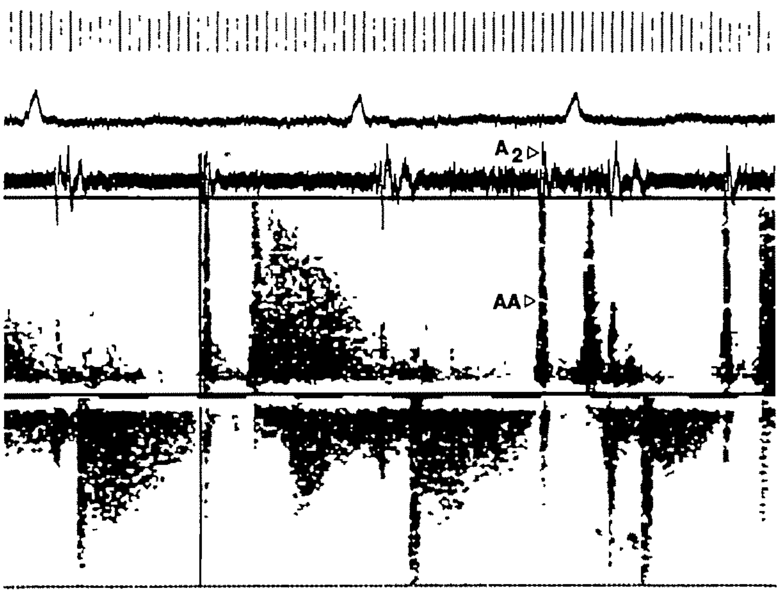

Figure 3 Continuous wave Doppler echocardiogram from a patient with mitral stenosis and atrial fibrillation showing both the aortic valve closure artefact (AA) and the onset of transmitral flow. The leading edge of the aortic closure artefact is synchronous with the onset of the first high frequency deflection of the second sound (A_2). Full scale deflection = 4 kHz.

Measurement reliability was tested by random selection of 10 sets of records and the measurements were repeated without prior knowledge of previous results. The measurements were highly reproducible, with mean (SD) interobserver variation of 5 (5) ms.

STATISTICAL ANALYSIS

We calculated the mean (SD) values for the measurements of isovolumic relaxation time and expressed them to the nearest 5 ms. Differences between the isovolumic relaxation time were analysed by the paired *t* test. The 95% confidence intervals were also calculated for the differences between their mean values. Possible correlations between the delay in the onset of flow in relation to mitral cusp separation and age, RR interval, and the interval from A_2 to mitral cusp separation were examined by Pearson's coefficient of correlation.

Results

ISOVOLUMIC RELAXATION TIME (TABLE 1 AND TABLE 2)

Healthy individuals

The interval between A_2 and mitral cusp separation was consistently less than that between A_2 and the onset of flow. The interval from cusp separation to the earliest detectable mitral flow was consistently greater than zero (25 (10) ms) ($p < 0{\cdot}0001$). The mitral valve artefact consistently followed (by 25 (10) ms) the onset of flow ($p < 0{\cdot}0001$). The leading edge of the aortic closure artefact was synchronous with the onset of the first high frequency deflection of the second sound recorded on the phonocardiogram and the interval between this artefact and the onset of flow on continuous wave Doppler was identical to that determined by pulsed mode.

Left ventricular hypertrophy

The mean values for the M mode and Doppler measurements were similar to those of healthy individuals. The scatter about the mean, however, was much greater. In 11 patients with coordinate relaxation (minimum left ventricular dimension to mitral valve opening <30 ms) the difference between the onset of transmitral flow and mitral cusp separation was 15 (10) ms, while in 10 patients with incoordinate relaxation (minimum cavity dimension to mitral valve opening interval >30 ms) the difference was larger (40 (11) ms).

DILATED CARDIOMYOPATHY

This group of patients had the shortest interval between A_2 and mitral cusp separation. The interval between A_2 and the onset of flow, though shorter than that in healthy individuals, was much longer than the interval between A_2 and mitral cusp separation. There was a delay of 50 (35) ms between mitral cusp separation and the onset of transmitral flow.

MITRAL STENOSIS

The M mode and Doppler measurements of isovolumic relaxation time were all shorter than those of healthy individuals. There was no

Table 1 Measurements (mean (SD)) of isovolumic relaxation time

Group	*A_2 to mitral cusp separation (ms)*	*A_2 to onset of flow (ms)*	*A_2 to mitral valve artefact (ms)*	*Aortic valve artefact to onset of flow (ms)*
Healthy individuals	60 (15)	85 (15)	115 (25)	85 (25)
Left ventricular hypertrophy	65 (25)	90 (30)	110 (25)	90 (15)
Dilated cardiomyopathy	15 (30)	65 (40)	90 (25)	65 (25)
Mitral stenosis	50 (25)	55 (30)	80 (30)	55 (20)

Table 2 Differences between measurements

	A_2 to onset of flow and A_2 to mitral cusp separation			*A_2 to mitral valve artefact and A_2 to onset of flow*		
Group	*Difference (ms)*	*p value*	*95% confidence interval (ms)*	*Difference (ms)*	*p value*	*95% confidence interval (ms)*
Healthy individuals	25 (10)	<0·0001	19–33	25 (10)	<0·0001	15–40
Left ventricular hypertrophy	25 (15)	<0·005	8–40	20 (20)	<0·01	5–40
Dilated cardiomyopathy	50 (35)	<0·0001	32–72	15 (10)	<0·05	10–35
Mitral stenosis	5 (5)	>0·05	−14–27	15 (5)	<0·05	−14–53

P values show significance of differences between measured intervals and zero.

Table 3 Coefficients of correlation

Group	*Flow delay v* *A_2 to mitral cusp separation*	*Flow delay v age*	*Flow delay v* *RR interval*
Healthy individuals	−0·221	0·132	−0·091
Left ventricular hypertrophy	0·016	0·453*	0·453*
Dilated cardiomyopathy	−0·271	0·227	−0·028
Mitral stenosis	0·020	−0·539*	−0·007

Flow delay = interval from A_2 to onset of flow minus interval from A_2 to mitral cusp separation.
*$p < 0·05$.

significant delay in the onset of transmitral flow after mitral cusp separation (5 (5) ms). The mitral valve artefact also followed the onset of flow in these patients but the difference was not significant.

CORRELATIONS (TABLE 3)

The delay in the onset of transmitral flow after mitral cusp separation showed no significant correlation with the interval between A_2 and mitral cusp separation. A weak correlation was seen between the delay in flow and age in patients with left ventricular hypertrophy or mitral stenosis, and between the delay in flow and RR interval in patients with left ventricular hypertrophy.

RELATION BETWEEN MITRAL VALVE ARTEFACT, MITRAL E POINT, AND DOPPLER PEAK FLOW (TABLE 4)

The mitral valve artefact did not correspond with the mitral cusp separation, which occurred before the onset of flow. Instead, the mitral valve artefact coincided closely with the E point of the mitral echogram, both in healthy individuals and in the patients. The peak transmitral flow velocity detected on Doppler occurred about 60 ms after the valve was fully opened, while the mitral valve was actually closing.

Discussion

When he originally defined isometric relaxation time, Wiggers regarded mitral valve opening and the onset of transmitral flow as synonymous. This assumption was not affected when the name was later changed to isovolumic relaxation time. More recently, many others, including us,[6] have also assumed that the time from A_2 to mitral valve opening measures the isovolumic relaxation time unambigously. But this is not so. Several experimental studies showed significant discrepancies between mitral valve motion and transmitral flow. Tsakiris *et al* marked the anterior mitral valve leaflet of dogs with radio-opaque clips and correlated motion of the marker with simultaneous high fidelity intracardiac pressure monitoring.[7] They showed that the point of mitral cusp separation preceded the diastolic pressure crossover (when ventricular pressure fell below atrial pressure) and thus the onset of flow by 5–60 ms.[7] Pohost *et al* also saw this delay.[8] In dogs with radio-opaque markers on the mitral valve to show leaflet motion, contrast medium injected into the left atrium flowed beyond the free edges of the mitral valve 43 (3) ms after the initial separation of anterior and posterior leaflets and it did not begin to mix with left ventricular blood until the valve was almost fully open. Estimates of isovolumic relaxation in man made angiographically, when "mitral valve opening" was marked by the first appearance within the ventricular cavity of unopacified blood from the left atrium, again gave normal values that were consistently longer than those measured in the same laboratory by M mode echocardiography.[9] A previous study in healthy individuals by a technique similar to ours showed some delay in Doppler flow after mitral valve opening, although the difference was much smaller (5 ms).[10] Although the mechanisms underlying mitral cusp separation are not clear,[11] mitral valve opening must thus be regarded as potentially separate from the onset of transmitral flow.

Until recently, isovolumic relaxation time was measured by M mode echocardiography. Now it is increasingly determined by Doppler echocardiography. The details of the technique were often not specified but seem to have used either the onset of forward transmitral flow or the mitral valve opening artefact[12] as the landmark for mitral valve opening. These measurements have all been called the isovolumic relaxation time, which implies that they are all equivalent. Our results, however, show that both in healthy individuals and in patients with heart disease, mitral cusp separation consistently precedes the onset of flow, which itself precedes the appearance of the mitral valve opening artefact. Indeed the mitral valve artefact coincides closely with the E point of the mitral echogram and thus the fully open position of the valve. While the intervals between A_2 and mitral cusp separation and A_2 and onset of flow, though consistently different, do fall within Wiggers's original definition of

Table 4 Relation between valve artefact, mitral E point, and Doppler peak flow

Group	*A_2 to mitral E point (ms)*	*A_2 to mitral artefact (ms)*	*A_2 to Doppler peak flow (ms)*
Healthy individuals	130 (20)	115 (25)	180 (25)
Left ventricular hypertrophy	120 (30)	110 (25)	170 (35)
Dilated cardiomyopathy	90 (30)	90 (25)	140 (45)
Mitral stenosis	90 (25)	80 (30)	Not available

isovolumic relaxation, the interval between A_2 and the mitral valve artefact does not, because it includes a significant portion of the rapid filling period.

Spectral analysis of Doppler signals introduces potential errors in the timing of flow. Analysis of very low frequency shifts takes a finite interval that may introduce error. We therefore used a lower filter of 250 Hz throughout our study and took the onset of flow as the first recordable signal above this level. Extrapolation of the spectral display to the zero flow baseline, which assumed constant acceleration, suggested that any delay introduced by this method cannot be more than 5 ms. The lack of significant delay in signal analysis is also supported by the observation that in patients with mitral stenosis, the onset of flow was effectively synchronous with mitral valve opening. The onset of transmitral flow recorded by the pulsed mode also coincided with that determined by continuous wave Doppler echocardiography, indicating that the timing of the onset of flow was not affected by the position of the sample volume. We conclude therefore that technical factors cannot explain our observations; mitral cusp separation, the onset of transmitral flow, and mitral valve artefact follow one another in an ordered sequence and cannot be regarded as synchronous.

In the group with left ventricular hypertrophy the mean values of isovolumic relaxation time and the delay in flow were the same as in the healthy individuals, although the scatter was greater. When relaxation was incoordinate, however, there was a much longer delay in the onset of flow after mitral cusp separation. The delay in the onset of flow may thus be an indicator of this aspect of diastolic dysfunction. The patients with dilated cardiomyopathy would be expected to have high left atrial pressure, and thus a short isovolumic relaxation time.[13] This was indeed the case; these patients had short intervals between A_2 and mitral cusp separation and between A_2 and onset of flow. There was, however, a large difference between the two measurements, probably because 22 of the 24 patients had functional mitral regurgitation. This persisted for more than 50 ms beyond A_2. Because forward flow cannot occur during regurgitation, the onset of transmitral forward flow is considerably delayed.[14]

As well as simply dealing with the methods of measuring isovolumic relaxation time, our results may be of more fundamental pathophysiological importance. We have previously suggested that restricted left ventricular filling time may be an important cause of diastolic dysfunction and its increase with the fall in heart rate may account for the therapeutic effect of β blockade in some patients with severe left ventricular disease and functional mitral regurgitation.[14] It now seems that the onset of transmitral flow may be delayed after mitral valve opening not only in patients with functional mitral regurgitation but also in those without, especially when relaxation is incoordinate. This delay may well restrict left ventricular filling time when heart rate is increased with exercise, causing stroke volume to be limited by a purely diastolic mechanism that is independent of any systolic disease that may be present.

The term "isovolumic relaxation time", even in terms of the original definition of Wiggers, is ambiguous. Details of measurement must be given in full, since not only do the various methods give results that are numerically different, but they are quite distinct in their pathophysiological significance. The delay in the onset of flow after mitral cusp separation, although predictable in healthy individuals, may vary widely in disease and may come to occupy a considerable proportion of the potential filling time. It may thus be a potentially major cause of diastolic dysfunction when the heart rate is rapid. The M mode and Doppler derived measurements should thus be regarded as complementary and be studied together, rather than separately, to increase our understanding of these complex early diastolic events.

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BRITISH CARDIOLOGY

Can rationing of cardiological services be rational?

Douglas Chamberlain, Richard Alderslade

In the United Kingdom there is a pervading perception that provision of health resources has not kept up with the availability of effective clinical procedures. By international standards expenditure on health services expressed as a percentage of gross domestic product remains low.[1] To clinicians the system feels increasingly tight financially because resources are not available to meet expressed clinical demand. This is particularly true of cardiology and cardiac surgery where the National Health Service (NHS) can no longer afford many effective treatments for all who might benefit from them. This harsh fact is often a source of disappointment and frustration. It can also cause conflict between professional groups who struggle to maintain their own service needs against competing interests. Is the problem inevitable? If it is, can we distribute resources in a manner that is seen to be equitable and fair?

Background

The reasons for the shortfall in provision are manifold, but innovation is the most important—and of special concern in cardiology because the pace of progress has been spectacular. Some cardiologists still active in the discipline were practising when digitalis, quinidine, nitrates, mercurial diuretics, and hexamethonium were the only specific remedies available for heart disease. Surgical options comprised closure of a patent ductus, Blalock anastomoses, and relief of mitral stenosis by digital splitting of fused cusps. Now the available drugs include increasingly specific modulators of myocardial, vascular, and autonomic function, angiotensin converting enzyme inhibitors, antilipidaemic agents, antiarrhythmics, and thrombolytics; all are highly effective but many are very expensive. Interventional cardiology has seen the growth of angioplasty over a decade as well as the slower development of balloon dilatation of valves. Implantable devices have become ever more complex with dual chamber pacing now commonplace, antitachycardia pacemakers gaining acceptance, and implantable defibrillators poised to play a role in the United Kingdom as they do already in the United States. Cardiothoracic surgeons have been busy for 20 years with coronary grafting but now many are turning to complex antiarrhythmic surgery and transplantation. Many of these developments demonstrably improve prognosis; all are impressive in terms of symptomatic relief. But every new advance increases the dilemma of cardiologists and cardiothoracic surgeons who work to a budget that is set by political and administrative considerations rather than by expressed clinical needs.

Other factors have compounded the economic penalties of innovation. First, important demographic changes are occurring in Britain. The fall of birth rate over the past 25 years together with the growth in the proportion of the elderly has reduced appreciably the percentage of the population who contribute directly to national wealth. The budget for the care of the elderly has grown; new and expensive procedures are increasingly in demand. As age increases beyond 75 years the average medical costs of caring for the elderly increase significantly; the proportion of the population within this bracket has increased by 28·4% in the past 10 years.[2 3] These trends will continue. A second factor adding to the cost of innovation is the increased expectation of a public with a keen appetite for media coverage of medical developments. General practitioners contribute as well, both because of increasing knowledge of recent progress and because one impressive medical or surgical result tends often to trigger several similar referrals. Finally, medical inflation has outstripped general inflation, partly because the health service is labour intensive and salaries have risen in real terms.

The shortfall in cardiological services within the United Kingdom is greater than many perceive. Provision remains grossly uneven and where little is provided expectation remains low. This is no justification for continuing inactivity. We believe that it is inappropriate that in 1988 45 of 210 health districts in England and Wales did not have a trained cardiologist[4] or that over 2 million people identified in an earlier survey had no immediate access to temporary pacing for countering a life threatening emergency.[5]

The argument that Western Europe as a whole has more than seven times as many cardiologists proportionally than the United Kingdom and that the United States has 10 times more may not be a strong one.[4] But it may be relevant to ask whether financial constraints were, historically, the only reason for this disparity? Perhaps they were not. In the United Kingdom we have currently a system that is neither directly responsive to market forces nor subject to strict central control. Priorities are determined at a local level by a process that is administrative and locally "political", often without a full appreciation of the weight of competing needs.

Even such provision as is available may not

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be used efficiently. In strictly economic terms it makes little sense to equip a catheter laboratory at a cost of over £500 000, yet see it inadequately staffed by radiographers, technicians, and nurses so that plant lies idle for many daytime hours: a situation familiar enough in many cardiac centres. Within district general hospitals the implications of such poor support are less dramatic but equally disruptive of the service. Almost always levels of technical staff are below reasonable recommendations; occasionally these staff are not provided at all. Simple but essential equipment such as treadmills often remains idle because physiological measurement technicans are scarce. So too is secretarial help.

Such critical limitation of resources has another serious implication: the expensive resource of cardiological skill may be inhibited or misdirected to inappropriate tasks. Undue priority may be given to some tasks at the expense of others that may be as essential but less urgent. Within catheter laboratories emergency procedures are displacing urgent cases from the waiting list; the pressure is compounded by the need to introduce angioplasty without extra resources being available. In the district general hospital crisis management displaces any resolve to introduce service improvements; for example, very few hospitals have rehabilitation programmes or adequate resuscitation training although the need for such facilities is not contentious and the cost modest.

At the academic level within cardiac centres and academic departments a major priority has become the preservation of research capability: thus studies that are economically safe—notably those financed by pharmaceutical companies—can take precedence over the pursuit of more fundamental research. Risk is an invariable component of true innovative research work, but risk is a luxury that few research directors can now afford.

Solutions

Is more money likely to be forthcoming? How satisfied are we that the money we currently have available is always being used wisely? How rational is its distribution? How will future changes (for example the implementation of the white paper *Working for Patients*[6]) affect this situation of perceived scarcity? How should cardiologists respond now and in the future to their current difficulties?

Before attempting to answer these questions, two processes need to be understood: allocation and rationing. Their edges are often blurred. But it is important to consider them separately, with allocation as the key issue. Allocation within a publicly funded system such as the NHS is a political and administrative process. The government decides how much it will commit to the NHS against other competing demands and the Department of Health, the regional health authorities, and district health authorities allocate resources in an attempt to provide a volume of resource across their entire range of statutory responsibilities.

This process of allocation is often confused with rationing. Rationing accepts a given allocated volume of resource and attempts to achieve a defined objective: the maximum beneficial health effect within a given scale of provision. Within the NHS rationing has always been a clinically based activity. Decisions on priority for admission and treatment are made by clinicians according to clinically determined criteria. This responsibility is the other side of the coin of clinical freedom. The stringency of rationing depends on the adequacy of allocated resources and fairly modest increases in allocation, particularly if sustained, might remove many of clinicians' current problems.

How rational can we make allocation? The truth is that since the 1950s health has been relatively well treated compared with other major publicly funded sectors,[1] and it is probably unreasonable to expect that public funding of the NHS will increase in real terms by more than 1–2% a year, despite a widely shared perception of need. Total expenditure on health could be increased by a greater reliance on the private sector and charitable and voluntary resources. There is also the drive within NHS management towards greater efficiency and productivity in the use of available resources.

The decisions taken by regional and district health authorities on the allocation of funding to cardiological and cardiac surgical services are influenced by three mechanisms.

POLITICO-VOCAL MECHANISM

The politico-vocal mechanism—"who shouts loudest gets most"—has a long and distinguished tradition. It encompassess the use of "political" pressure groups, including public sympathy and emotion. In a service where the objectives are set by political considerations and considerations of personal value, there may be no alternative to being guided by the process described as "disjointed incrementalism".[7]

RATIONAL-DISTRIBUTIVE MECHANISM

This originates with the perception that neither the providers nor the consumers of health care are competent to assess national need. The conventional response is to require epidemiologists and health system managers to identify these total population needs and establish programmes of service activity designed to secure health improvements. Some planners and managers believe that the introduction of any new technology should be supported by evidence from randomised controlled trials, but they may not always understand the limitations of such trials. Trials offer the best guidance we have for the efficacy of treatment but there is often room for a different interpretation and rejection of what may seem definitive conclusions. Moreover, trial results are never wholly relevant to an individual patient with his or her own unique set of pathological and functional problems.

Despite these uncertainties, planners and managers also increasingly expect additional evaluative information, which can be equally difficult to provide and interpret. They want to know not only that a procedure is effective but also *how* effective and at what cost. Cost utility analysis is one method designed to consider the cost of new technologies against their potential global population benefit. Mortality benefit is adjusted for the quality of life during the life years gained by the application of the technology. This measuring tool is termed the QALY—Quality Adjusted Life Year. There are various difficulties associated with this approach and it has received substantial criticism.

While the basic principle of cost-utility analysis cannot be challenged its implementation is more difficult than many believe. What is cost and how is it measured? Should judgments be made based on cost to the hospital or to the NHS? The two can be very different. Should we be concerned with marginal costs or full costs? Should costs be calculated per procedure or per case? Should the calculation be for this admission, this year, or forever? Even if the guidelines are agreed, measurement is complex, as wide disparities in data (for example the cost of coronary artery bypass grafting) can attest. How easy is it to estimate outcome? Many feel it is not easy, and that attempts to do so may lead to misleading distortions. Although the QALY is likely to become established as a permanent package within health economics, it is at best a crude measure and may be based on questionable assumptions.

Nevertheless, despite these limitations, the technique can be useful in guiding decisions on allocation and in extending the framework of "rationality" on which they are based. For example the results of ISIS–2 show the clinical effectiveness of treatment with streptokinase as well as aspirin after infarction.[8] It can be shown by cost-utility analysis[9] that the costs per QALY of adding streptokinase into the treatment required are low compared with those costs published for other procedures in routine use, including mammography, heart transplantation, coronary artery bypass grafting, and all types of treatment for end stage renal failure.[10 11]

MARKET ORIENTATION

A pure market orientation is inappropriate within health care provision because those most in need are often least able to pay. For this reason the proposals within the NHS white paper aim to continue to base funding largely upon taxation, with receipt of service remaining substantially free at the point of delivery. Publicly funded authorities will determine the health care needs of the population and will purchase services to meet those needs from a range of service providers, within both the public and private sectors. Increasingly these "purchasing" authorities will not manage services directly. "Providers" will deliver service against contracts established with the "purchasing" authorities; the competitive forces created within this marketplace are expected to create increased efficiency and eliminate the inefficiencies inherent in any large bureaucracy. The authors of the white paper believe that this greater efficiency will be associated with a better quality of care and that standards can be set and monitored within the contracts. A substantial investment will be necessary in information systems to support the contractual interface between purchasers and providers. Will the expected benefits be achieved? The answers to this question lie in the future, though the challenge is immediate.

The difficult way forward

It is clear that cardiologists and cardiac surgeons must be involved in decisions about both allocation and rationing if they are to influence these processes for the benefit of patients. Yet this object poses an inevitable dilemma. Should doctors face the costs of their decisions? If they do not, the result can be inefficiency and favoured provision of patient care for the few to the detriment of the many. If they do, then the result could theoretically be a downward pressure on the quality of service.

We have no easy solution. Most agree that the clinical views should be heard at the level of political allocation, at the level of local administrative distribution of the allocation using the most appropriate "rational" means, and within the unit itself, increasingly through an involvement in resource management. This involvement in resource management may reduce anomalies in the provision of health care but has little effect on the adequacy of allocation.

Clinicians must accept that if treatment of proven effectiveness is not available for all who may benefit, an element of rationing must be introduced if provision is to be better than random; but this poses considerable problems when dealing with individual patients. Physicians and surgeons are already familiar with triage as the technique invented by military surgeons for selecting battlefield casualties most likely to benefit from the application of scarce resources. But when this process has an economic basis it is less familiar and less welcome. It creates a even greater dilemma because it influences the doctor-patient relationship. The patient regards the physician as a trusted adviser, and expects him to be, where necessary, his advocate.

How can physicians combine their clinical roles with their responsibility for the use of resources? No one but the physician can make rationing decisions based on clinical criteria. Yet their actions must not damage their relationship with an individual patient. Again we have no ready answer, but only a part solution. Physicians will come to see that involvement in the processes of medical audit and resource management can lead increasingly to informed decisions based upon knowledge of outcomes that are translated into agreed protocols for service delivery. In this way doctors should not need to introduce budgetary considerations into clinical decisions about individual patients. They will recognise the position of their patient in relation to a would be glad if Professor Samojloff would send him reprints of his published works on the electrocardiogram." In addition to acknowledgments of reprints over the years, in a handwritten letter Lewis (15 August 1922) commented on a paper on atrial flutter by Samojloff, of which he had received a reprint, and discussed various interpretations of the cycles. But the most interesting letter is that sent in 1928, in which Lewis thanked Samojloff for the picture of Einthoven, which he also admired (fig 5).

The letters from Samojloff are reproduced with the permission of his daughter Anna Samojloff of Moscow and through the courtesy of the Trustees of the Wellcome Trust, whom we also thank for permission to mention the letter from Raymond Crawford to Lewis. We thank Professor R A Chapman, secretary of the Physiological Society, for permission to use material from their archives and Mr D H Steven, honorary archivist, for the list of those attending the Society's Harvey celebration, used in figure 3. Mr Geoffrey Davenport, librarian, Royal College of Physicians, kindly provided details of the College celebration.

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LETTER TO THE EDITOR

- *The British Heart Journal welcomes letters commenting on papers that it has published within the past six months.*
- *All letters must be typed with double spacing and signed by all authors.*
- *No letter should be more than 600 words.*
- *No letter should contain more than six references (also typed with double spacing).*

Estimation of the risk of death after acute myocardial infarction from systolic time intervals

SIR,—Dr B J Northover's study (1989;62: 429–37) adds a critical link to the chain of evidence supporting the use of the systolic time intervals, specifically the ratio of the pre-ejection period to the left ventricular ejection time (PEP/EP), as a valuable mortality risk indicator after acute myocardial infarction. In an earlier investigation on 578 patients with acute myocardial infarction, Northover showed that the PEP/EP ratio was a potent predictor of the risk of death during the in-hospital treatment period.[1] In the recent study, Northover followed for 51 weeks 600 patients who had survived the first seven days after acute myocardial infarction. Again the PEP/EP ratio was a good indicator of the risk of death. The PEP/EP ratio has been shown to be an independent indicator of the risk of death in patients studied 14 months to 6 years after acute myocardial infarction,[2] which suggests that the PEP/EP ratio retains its prognostic potency for at least the first 6 years after acute myocardial infarction.

In the recent Northover Study multivariate analyses of the predictive power of the PEP/EP ratio and a host of clinical prognostic indicators showed that the PEP/EP ratio and five clinical descriptors including the number of previous myocardial infarctions, diabetes mellitus, age, diuretic treatment, and bundle branch block retained maximal prognostic power. Among these the PEP/EP ratio clearly had greatest prognostic impact. In the patients studied between 14 months and 6 years after acute myocardial infarction,[2] univariate analysis showed that the PEP/EP ratio and age > 60, angina pectoris, dyspnoea, previous myocardial infarction, presence of S3 gallop, and cardiomegaly on chest radiograph were significant prognostic factors and that the PEP/EP ratio was the strongest prognostic factor.

Northover examined 24 hour rhythm monitoring tapes and the signal averaged electrocardiogram as electrophysiological variables that may provide independent mortality risk discriminating power. None of the commonly tested rhythm disturbances added independently to mortality risk after allowance for the PEP/EP ratio and the five clinical descriptors noted above. The occurrence of late potentials on the signal averaged electrocardiogram, which showed a significant independent univariate association with mortality, did not augment the mortality risk discriminating power of the PEP/EP ratio combined with the five clinical descriptors listed above.

These observations draw attention to the potency of the PEP/EP ratio as an indicator of mortality risk in patients with recent and remote myocardial infarction. The high sensitivity (88%) and specificity (96%) of the PEP/EP ratio in detecting abnormal and normal global ejection fraction in patients with previous myocardial infarction[3] supports evidence that these measures may be equally potent discriminators of mortality risk As yet we do not know whether the PEP/EP ratio adds significantly to or substitutes for the ejection fraction measurement in mortality risk discrimination.

I congratulate Dr Northover for his singular effort in contributing evidence that a measure of ventricular function, other than the global ejection fraction, can provide more potent mortality predictive power than commonly applied clinical descriptors; this relatively inexpensive approach to the assessment of ventricular function seems to be a better predictor of risk than 24 hour rhythm monitoring and the signal averaged electrocardiogram.

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1 Northover BJ. Left ventricular systolic time intervals in patients with acute myocardial infarction. *Br Heart J* 1980,43:506–13.
2 Weissler AM, O'Neill WW, Sohn YH, Stack RS, Chew PC, Reed AH. The prognostic significance of systolic time intervals after recovery from myocardial infarction *Am J Cardiol* 1981;48·995–1002
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BOOK REVIEWS

William Heberden. Physician of the Age of Reason. Ernest Heberden. (Series: Eponymists in Medicine) (pp. xiv + 246; £12.95 hardback; £7.95 softback) London: Royal Society of Medicine Services, 1989. ISBN I-85315-116-5.

Great biographers not only write about their subjects but in a sense become the subjects. The writer must be immersed in the appropriate time and place, recognising that subsequent historical changes may influence present interpretation. If written or oral records are sparse, the author cannot penetrate the mind and heart of the subject of the biography. Then the alternative choices are adherence to established facts, with speculation about what has come to be called "soft" data, or historical fiction. To some extent all biographies are historical fiction, for the characters portrayed exist only in the imagination of the writer.

Ernest Heberden is the fifth generation descendant of William Heberden, the eighteenth century physician. In view of Heberden's eminence as a London practitioner, the respect in which he was held by colleagues and the general public, his original medical contributions, and his popular "Commentaries on the History and Cure of Diseases" it may seem surprising that no full-scale biography has been written previously. Ernest Heberden admits limited knowledge of his distinguished ancestor before his investigation and "no family archives," but he did an exhaustive search of historical records, William's publications, and his available preserved letters. Despite this diligent pursuit, the elder Heberden escapes the firm grasp of the biographer. One is forced to conclude that William Heberden wished to obscure his personal life and that of his family. Neither he nor his son, William, disclosed much information that could not have been gathered from other sources. William Heberden had famous and influential friends in and out of his profession, but apparently few intimates. His friends made numerous references to his pleasing personality, hospitality, calm judgment, rectitude, frankness, erudition, clarity, modesty, and religious faith as well as his professional ability. Heberden was the personal physician of two insightful and highly critical observers: Samuel Johnson and John Hunter. It is possible that none of his distinguished friends felt that they knew the inner man well enough to undertake a biography or that he dissuaded them. Certainly, he outlived most of his contemporaries and he may have so awed younger men that none attempted a biography.

The bare facts of Heberden's life are impressive. He was a poor London boy who had the good fortune to be stimulated by an inspiring grammar schoolmaster who pushed him into study of classic languages and arranged his entrance into Cambridge University at the age of 14. He continued his scholarly studies, mastering Latin, Greek, and Hebrew, as well as other academic subjects. Deciding to study medicine at Cambridge, he spent some time in an unspecified London hospital. He was permitted to accelerate his programme and was awarded the MD degree at the age of 27. William remained at Cambridge, teaching materia medica and seeing local patients. After a decade, he moved to London and met with early success in practice.

Although London had several prominent surgeons on the staffs of various hospitals, most of its well known physicians saw patients in the physician's home, in the patient's home, or in coffee houses. Heberden did not approve of medical education in London hospitals, but he was powerless to change the system. His admirable qualities were recognised quickly by colleagues and patients and soon he was considered to be one of London's leading physicians. The author traces William Heberden's rise to the top of the profession as well as his invaluable contributions to the Royal Society and the College of Physicians. He was instrumental in organising publication of the *Medical Transactions of the College of Physicians* and read numerous papers before the college, both original and communications from friends or acquaintances. Heberden enrolled in what he knew was an unpopular cause: the right of Dissenters (those not members of the Church of England) to join the College of Physicians.

Many of these were graduates of the University of Edinburgh, one of the outstanding medical schools of all Europe. The cause failed and the rights of Dissenters were denied for another 100 years. Although William was a dedicated member of the Church of England, he did not hesitate to annoy a minority of the lesser clergy and most of the bishops by his forthright stance on Dissenters. Heberden had the ability to challenge stands of his friends on important principles without alienating them.

Heberden was the first to separate chickenpox clearly from other exanthems and described the arthritic knobs of the distal phalanges, and his description of angina pectoris in 1768 is one of the classics of medicine—so complete that little has been added since. Here he shows his modesty in referring to a friend (probably Dr John Fothergill) who had recognised the condition for some years. He was not aware of the cause of the symptoms and had not had the opportunity to observe a postmortem examination in a case. After an abstract of his description of angina was published in *Critical Review* in 1772, a reader (probably not a physician as stated) recognised the similarity to his own symptoms and realised the likelihood of sudden death. He wrote to Heberden saying that he wished a postmortem examination to be arranged in the event of his sudden death; this request was fulfilled a few weeks later by Heberden who enlisted the services of John Hunter, the leading British surgeon and pathologist. Although the biographer doubts that William Heberden and Edward Jenner had ever met, both were present at this necropsy, Jenner being Hunter's assistant at the time. Nothing was found to account for the symptoms, but Jenner, reflecting on the episode years later, doubted that the coronary arteries had been examined. Heberden did not think that angina was associated with an anatomical abnormality. Despite this belief, he presented a paper submitted by Dr John Wall to the College in 1772, in which Wall attributed angina to aortic stenosis in a single case examined pathologically. Heberden's reading of Wall's contribution to the college is a demonstration of his objectivity and generosity, even when he did not agree with the conclusion. Later, Jenner related angina pectoris to coronary artery disease and wrote to Heberden about his observations. The biographer quotes Baron (1838) as saying that the letter (incorrectly dated 1778 instead of 1786) was never posted, but Otterly (1839) said that it was. In 1799 Parry published his excellent book on angina pectoris, giving strong support to the ischaemic theory. Black had published a similar view in 1795. There is no evidence that Heberden ever recognised the cardiac seat for the symptom. In his commentaries, Heberden repeated his description of angina, but this was written at a much earlier date (writing completed in 1782).

The commentaries were written in Latin for the benefit of any of his sons who might choose medicine as a career. His son, also William, translated the text into English and published it in 1802, the year after his father's death. There is no doubt that the elder Heberden's modesty about this contribution delayed its publication for a generation. The commentaries received immediate and lasting acclaim in Britain and abroad.

William Heberden made perceptive observations on vital statistics, disposal of human wastes, sanitary water supplies, prudent dieting, polypharmacy, the inefficacy of most medicines then available, optimum age for retirement, and medical education, both undergraduate and postgraduate. He recognised the dangers of tobacco, alcohol, and opium, but advised that opium should not be withheld in hopeless cases in which it could give relief. He deserves a place in medical history for even these "minor" contributions. In addition to reading classic languages, he was interested in current literature and was an amateur astronomer. He and his companions, John Hunter and John Fothergill, were friends of Benjamin Franklin, and Heberden and Fothergill were sympathetic to the American cause in the revolution. Heberden was a keen observer and critic, but he was not a scientist in the mould of two friends, Stephen Hales and John Hunter, nor the much younger Edward Jenner.

The author has written a creditable biography in view of his ancestor's modesty and taciturnity about personal affairs and the lack of information that might have been supplied by his contemporaries. William Heberden stands partially revealed after almost two centuries, despite his apparent desire for obscurity. Ernest Heberden has served the medical public well in not honouring this wish in view of the greater good. All who are interested in William Heberden or in British medicine in the latter half of the eighteenth century will want to own this book. There is an excellent set of references for each chapter and the index is accurate and valuable. A sketch of William Heberden, the younger, follows the biography.

WILLIAM L PROUDFIT

An Unquiet Life: Memoirs of a Physician and Cardiologist. J F Pantridge. (pp. xix + 122; £9.95.) Antrim, Northern Ireland: Greystone Books, 1989. ISBN 1-870157-07-9. We have been asked to point out that this book is no longer available from Greystone Books. Copies should be ordered from: The Secretary, The Heart Fund, Institute of Clinical Science, Royal Victoria Hospital, Belfast BT12 6BA, or from bookshops in Northern Ireland.

Cardiologists world wide will know or know of Frank Pantridge as one of the "personalities" of our specialty in the postwar years, and also as the father of pre-hospital care for myocardial infarction. Pioneers do tend to have similar attributes that command attention: not only originality but boundless energy, dogged determination, and a readiness—with suitable provocation—to show disrespect for the establishment. These qualities come blazing through this fascinating book with a terse incisiveness that is so characteritic of the author.

This is not an autobiography but a collection of reminiscences as the subtitle suggests. It is written for the general reader. If cardiologists find a particular fascination with the book it will be because they learn more of the man and not because the contents have any narrow interest. They do not. Pantridge the cardiologist hardly emerges until the last 30 pages. After some insights into his student years we have two harrowing chapters on the author's war experience first as a medical officer in Singapore and very soon as a prisoner of the Japanese. Some of us old enough to remember those dark days still need reminding that incredible incompetence allowed 30 000 Japanese to defeat 85 000 allied troops who were given little chance to defend what should have been an impregnable fortress. And that in one camp only 182 of 1600 British prisoners survived the war (most camps were little better). As we read of the atrocities and of the privations that were suffered by those who were captured, we can only marvel at the spirit that kept any of them alive. How easy to understand why Pantridge remains full of anger after so many years—anger on account of the many he strove to help but who died under terrible conditions and seemingly so needlessly: colleagues, friends, strangers from other lands. But of self pity there is none. Indeed Pantridge makes the point that such experiences can even be salutary; but only an indomitable character could remain sufficiently unscathed to emerge the tougher for such an apprenticeship to life.

I first encountered Pantridge in 1968 after a lecture on the new concept of pre-hospital care that was given at the Massachusetts General Hospital where I was then working—a meeting that made more impression on me than it would have done on him. Alone of the audience, I was unimpressed and deeply sceptical. A prophet is not recognised in his own country, but neither is he recognised by his own countrymen. It was fate rather than insight that led to my own conversion to the cause a year or so later. I was not the last, and indeed only recently has the value of Pantridge's work been widely appreciated in Britain. Even now, Pantridge himself has not received the acclaim that might seem appropriate for one who has made such a major contribution; perhaps the very characteristics that enable a man to modify strongly held views among his peers are the ones least likely to earn the reward of recognition.

This little book remained too long on my shelf with other tasks that await convenient moments that so rarely come. But once I had opened it I found it was no chore. It was full of interest, and I have profited from having read it. Others will feel the same.

DOUGLAS CHAMBERLAIN

In Search of Truth. A Portrait of Don Craib. E B Adams. (pp. xi + 123; £7.95 paperback; £12.95 hardback) London and New York: Royal Society of Medicine Services, 1990. ISBN 1-85315-118-1 (paperback); ISBN I-85315-119-X (hardback).

It would be easy to glance at this brief biography and label it as no more than an affectionate tribute to a mentor by a disciple but that would be wrong. True, it may be of more immediate interest to older graduates of the University of the Witwatersrand Medical School than to other readers, but some very important historical aspects of the development of electrocardiography are ventilated in this book. When eyes are focused on the political ferment in South Africa a reminder of other aspects of life in that country is timely.

William Hofmeyr Craib was part Scot, part Afrikaner: his middle name indicates his membership of an extraordinary family of intellectual distinction and political achievement now largely forgotten. Having served in the British army in France during the first world war, he stayed on to qualify in medicine at Cambridge and Guy's. A Rockefeller fellowship was taken in his stride and this took him to Johns Hopkins in 1925–6. There his earlier mathematical training led him into electrophysiological studies and he was just one step ahead of Frank N Wilson in propounding the doublet (dipole) hypothesis for cardiac activation. This work brought Craib to the attention of Sir Thomas Lewis when he returned to London in 1926, and he was persuaded to take up a Medical Research Council fellowship at University College Hospital. But for all sorts of reasons he seems to have got on badly with a host of luminaries, including Willem Einthoven and Lord Adrian. After completing an account of his studies that was published in 1930 as a Medical Research Council Special Report on electrocardiography, he abandoned London—and research—and returned to South Africa to undertake consultant practice in Johannesburg. Soon, despite local antagonism, he was appointed part time professor of medicine but was not given the full time chair when this was created at the end of the second world war. His latter years were occupied with practice followed by research administration; and then he recalled past glories and slights.

At this stage of his life Craib became a voluminous correspondent, apparently determined to correct historical errors and to justify himself; but the old adversaries were now gone. Adams gently agrees with those who have claimed that Craib had exaggerated some of the events. Indeed he received international recognition fifty years after his great days, as his letters were passed around. As he had given up research and writing for international journals, it was with some surprise that he was discovered by those who had continued along the lines that he and Wilson had laid down. It is particularly gratifying that Barry Adams qualifies some of the hostile memories that dominated Craib's last years and tries to get the balance right. Craib's ambivalent feelings about Lewis should be tempered by the knowledge that in reporting to the Medical Research Council that, despite Lewis's advice to the contrary, Craib was determined to resign, Lewis stressed that "..... I have regarded him for some while as one of the most, if not *the* most promising candidate (sic) for a professorship of clinical medicine and research in this country within the space of a few years." His departure was a great loss, but others took up the thread, and unipolar electrocardiography soon prevailed.

Craib was virtually forgotten outside South Africa and even there the importance of his early work was not fully appreciated; but this graceful account by one of his most distinguished pupils rectifies these omissions. Adams evades only two, perhaps impossible, questions. What might Craib have achieved had he remained in the mainstream? And was there some personal quirk that prevented him from following such a path?

DENNIS M KRIKLER

Br Heart J 1990;64:230

BRITISH CARDIAC SOCIETY NEWSLETTER

Administrative arrangements

We have made progress with the new committee structure. The Training and Manpower Committee that was formed last year in association with the Cardiology Committee of the Royal College of Physicians of London has been enlarged and will have much to do. It comprises Sleight, Cobbe, Hall, Webb-Peploe, and Silove for the Specialist Advisory Committee, Pentecost for the College, Julian for the British Heart Foundation, Petch as the European representative, with Henderson, Dymond, and Chamberlain as other representatives of the Cardiac Society. On the subject of training, several meetings have taken place with the Manpower Committee of the College (Chamberlain representing the society) in an attempt to resolve the problem of registrar posts. We are anxious to have enough posts protected for cardiology to support the new training programme. This is agreed in principle, but arrangements may be delayed because other specialties wish to follow the same path. This is reasonable, and indeed lends strength to the cause, but the logistics have become formidable Meanwhile the Department of Health is anxious to press ahead with the new arrangements to regulate registrar posts and reduce the numbers. You will hear more.

A Data Management Committee has been set up, to be chaired by Parker. Other members are Campbell, Hubner, Macfarlane, Nathan, Poloniecki (co-opted), Rickards, Chamberlain, K Taylor, and a paediatric cardiologist still to be nominated. This committee will have an interest in systems and in software, with the particular aim of achieving uniformity or compatibility wherever this is desirable. This is a hot potato—if you have strong views do not hesitate to make them known.

We need to be smarter with our public relations. Therefore the small publications committee has been expanded and will take on a wider role as Public Relations and Journals Committee. It will be chaired by Oldershaw, with Krikler (ex officio as editor of the *British Heart Journal*), Sleight (ex officio as editor of *Cardiovascular Research*), Henderson, Parker, Poole-Wilson, and Chamberlain. We have appointed Joan Scott Public Relations to assist us for a year in the first instance: this will provide a measure of the value of professional help in this important area. Staff within the organisation are no strangers to the medical scene. They have worked with the society in the past and have a regular commitment to several other specialist groups and to the British Heart Foundation. Claire Marley (Claire Julian in private life) is the consultant for the organisation who will work with us.

The society's contribution to the Joint Cardiac Audit Committee has been strengthened by the addition of Cobbe, de Bono, Hubner, Keith Fox, and Wray. Other members are Joy, West (co-opted), Treasure, and Chamberlain, with Brooks (chairman), Birkhead, and Pentecost as college nominees.

The name Chamberlain appears more than most—this is an ex officio phenomenon, and is not related to any desire for more work: still less to any special skills or popularity in committees. He is confident that others will carry the burdens. This is not the end of the list of new or expanded committees. We hope soon to appoint a Technicians Liaison Committee. It will be chaired by Dymond. Lastly, we want to explore the possible role of an Ethics/Peer Review Committee. Do other areas need special attention?

Annual meeting

By the time members read this page, the die will have been cast on the question of London meetings. The Conference Centre at Wembley has now offered what we were seeking but could not previously attain—agreement to hold meetings on alternate years at Wembley. But after Torquay do we still want it? If you do not already know and you cannot wait to find out by watching this space, you will have to telephone me and I will tell you. Perhaps we should settle other contentious issues by ballot: we cannot then be considered undemocratic, at least not in all things.

Europe

The European Society of Cardiology meeting in Stockholm will be taking place very soon after this appears in print. We hope as many as can do so will attend. The society will help with expenses of at least some registrars and research fellows if they are not sponsored by a pharmaceutical company. Preference, of course, will be given to those who will be presenting papers or posters. With a European meeting in the autumn, do we need a second low cost workshop type meeting for the society at a similar time of the year? Our affiliated groups tend to have their own meetings, and may not wish to be tied to a common venue and time. Is there really a need for more meetings to present hot data?

Henderson has asked whether it should be customary to use the initials FESC for those who have been elected to the European Fellowship. Surely we should—if indeed one is in degree, diploma, and fellowship mode. This is coming into use by our European colleagues, and will reflect our own support for the appropriate integration of European cardiology. The European Fellowship is becoming coveted, and this is the way we believe it should be. We now need some agreement both on the principles governing nominations for election to the Fellowship, and at what stage in the career structure this might be appropriate. At the present time some inconsistency between countries is emerging.

The society page

We want to air the views of members on this page. A little amicable controversy is not barred. Please be encouraged to write with news, comments, queries, and criticisms. We reserve editorial rights, but only on the ground of what we feel to be appropriate. We are not adverse to heterodox views, but remember that they will be firmly attributed to their authors, especially if we do not like them.

DOUGLAS CHAMBERLAIN
President, British Cardiac Society
PAUL OLDERSHAW
Secretary, British Cardiac Society
St Andrew's Place,
London NW1 4LB

NOTICES

British Cardiac Society

The Annual Meeting will take place at the Scottish Exhibition Centre, Glasgow, on 30 April to 3 May 1991.

Endovascular therapies in vascular disease

The International Congress IV: Endovascular Therapies in Vascular Disease will take place in Scottsdale, Arizona on 10 to 14 February 1991. Further information from Erika Scott, International Congress IV, PO Box 10,000, Phoenix, AZ 85064, USA.

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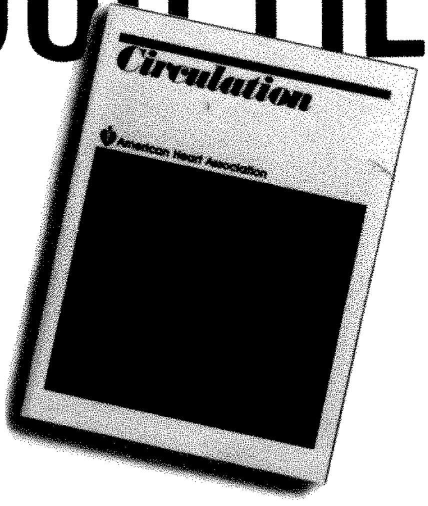

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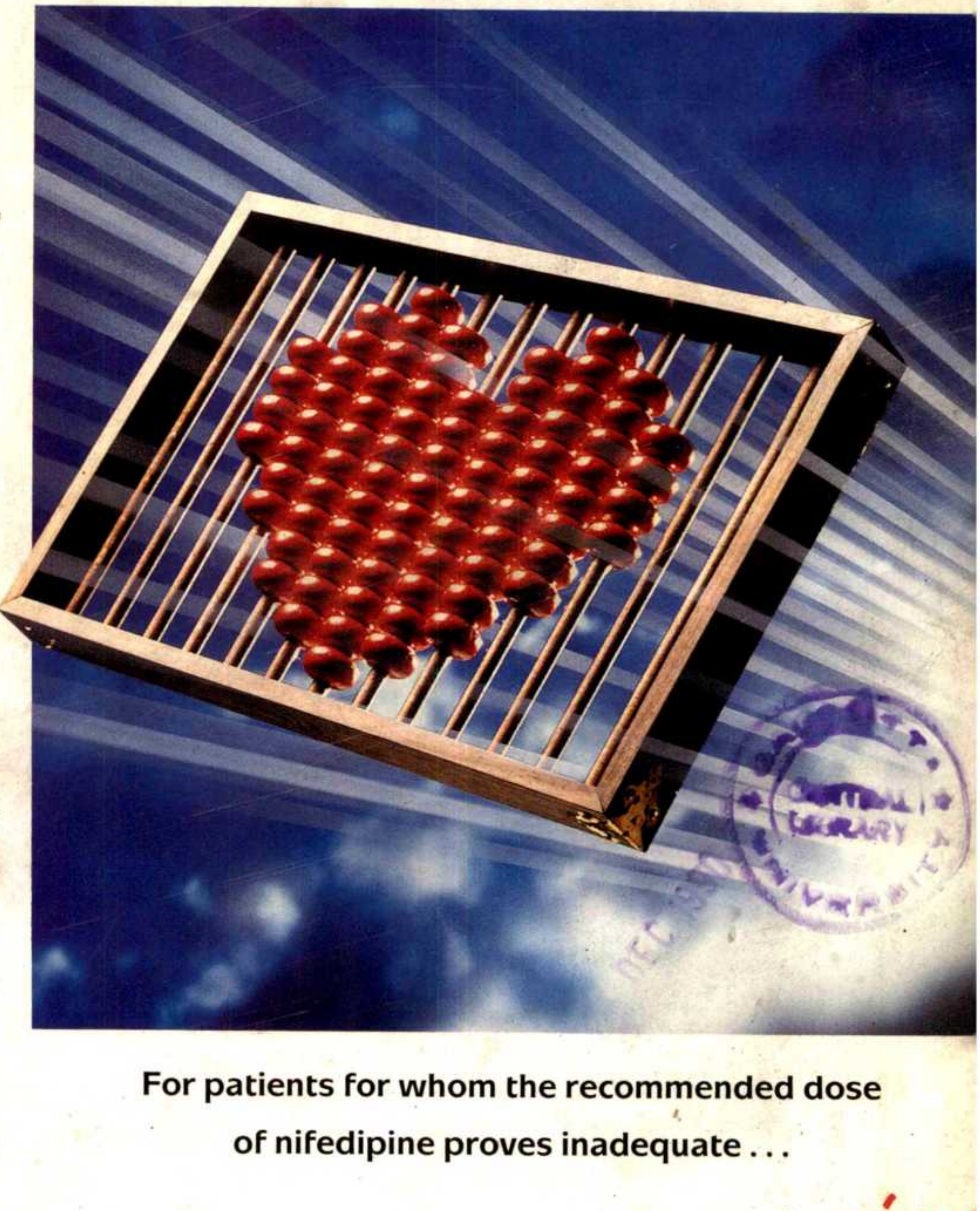

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In association with the British Cardiac Society

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NOTICE TO CONTRIBUTORS

Papers relating to the heart and circulation should be sent in triplicate to the Editor, British Heart Journal, BMA House, Tavistock Square, London WC1H 9JR, and be prepared according to the *Uniform requirements for manuscripts submitted to biomedical journals* (Vancouver agreement) (*Br Med J* 1988;**296**:401–5). Authors are asked to complete a copy of the checklist provided (1990;**63**:71–2 (January issue)) when submitting their manuscripts for publication. The reference number given on the acknowledgement postcard sent out by the editorial office should be quoted on all subsequent correspondence and telephone inquiries. A covering letter must be signed by all authors stating that they have seen and approved the paper and that the work has not been, and will not be, published elsewhere. All authors will be required to transfer copyright of their articles to the journal before publication. (All material for possible publication (including Letters to the Editor) *must* be typed in *double spacing* with 4 cm margins.)

ETHICAL STANDARDS

Authors are expected to comply with the code of ethics known as the Declaration of Helsinki. Where appropriate, manuscripts should include a statement that the research protocol has been approved by the locally appointed ethics committee and that the informed consent of the subjects has been obtained.

CASE REPORTS should convey only the essential facts of a case and the discussion and bibliography be kept to a minimum. They should have no more than three authors, should not exceed 1500 words, and include no more than two Figures.

ABBREVIATIONS should *not* be used in the text, except for mathematical calculations and units of measurement.

REFERENCES must be cited precisely according to the Vancouver agreement and be typed in *double spacing*. As a general rule, no more than three references should be cited for any one statement.

Authors are responsible for the accuracy of any references cited: these should be checked at source or with the listing in Index Medicus.

UNITS OF MEASUREMENT

All haematological and clinical chemistry measurements should be given as SI units. Blood pressures should be given in mm Hg. Measurements of length, height, weight, and volume should be reported in metric units and temperatures should be reported in degrees Celsius.

TABLES must be typed on separate sheets and not in the text. Titles should be provided, and all abbreviations used must be given in full in a footnote.

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BRITISH
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Editorial

Getting a handle on the prevalence of coronary heart disease

Few scientists are as skilled as epidemiologists at tormenting clinicians. The practice began when John Snow, an academic ruffian, damaged physicians' pride and public property by removing the handle of the Broad Street pump during a cholera epidemic.

In this issue of the *British Heart Journal* the contretemps continues (p 295). Smith *et al* confirm the high prevalence of coronary heart disease in Scotland and establish that there is considerable variation in disease prevalence among Scottish districts. This observation extends the earlier work of the Scottish Heart Health Study which showed regional differences in the death rate from coronary heart disease and in the prevalence of risk factors for ischaemia.[1-4] Understanding these variations in a country with one of the highest rates of coronary heart disease in the world may lead to a better understanding of preventable causes of coronary heart disease.

The difficulty that clinicians and epidemiologists have in communicating is illustrated by this paper and primarily centres on the methods used by Smith *et al* who estimate the prevalence of coronary heart disease. Unlike the "hard" data for rates of hospital admissions for infarction, prevalence is difficult to measure accurately and must be estimated by symptoms, by abnormalities in the electrocardiogram, or by other more specific tests. The Scottish Heart Health Study used several methods to estimate disease prevalence, including a self administrated Rose questionnaire for angina pectoris, a resting electrocardiogram coded by the Minnesota criteria for Q/QS patterns for past transmural infarction and by ST and T wave abnormalities for resting ischaemia, and a self-reported history of coronary heart disease. These are accepted techniques with good, population based, repeatability and validity for the detection of coronary heart disease. But they are also commonly used clinical tests that clinicians, for good reason, do not trust to diagnose coronary heart disease accurately in individual patients.

Because these methods are standardised they can be used to estimate disease prevalence in different large populations. Their limited sensitivity and specificity are outweighed by their repeatability when applied to the same group of people, their ease of use, and their proven validity in identifying groups of people at risk of developing the consequences of coronary heart disease. The methods work particularly well for testing hypotheses about associations between coronary heart disease and its potential causes because random misclassification of an individual as having or not having coronary heart disease tends to obscure true associations but not create false associations. For comparisons between different groups, random errors and even biases leading to overestimates or underestimates of the actual number of true cases of disease are less critical because the comparison is the measure of interest. Moreover, the use of all three methods allows the estimates by each method to be compared.

But the extent to which these methods can be applied to smaller groups—for example, to a Scottish district or to an individual—is unclear. For small groups of people and certainly for individual patients we need more sensitive and specific methods. For example, it would be ludicrous to label an individual as having coronary heart disease on the basis of their answers to the Rose angina questionnaire or ST and T wave abnormalities on their resting electrocardiogram.

Even the coded resting electrocardiogram, one of the more objective methods of assessing disease prevalence, is seriously flawed. Old myocardial infarctions can cause Q or QS waves in the electrocardiogram, and Q waves from an infarction may resolve. The relation between coronary heart disease and ST and T wave changes on the resting electrocardiogram is even less precise because these repolarisation abnormalities are likely to be caused by left ventricular hypertrophy or other commonly occurring cardiac processes.

A patient's self-reported history of a previous infarction or diagnosis of angina is also not specific for diagnosing ischaemic heart disease. Even for carefully recorded data, verification of self-reported history is not perfect. For example, a diagnosis of myocardial infarction can be confirmed in hospital records in only 85% of those with a self-reported diagnosis.[5] The validation of less definite end points is probably much less consistent.

How do these limitations in survey methods affect the results of the Scottish Heart Study? There seems to be reasonable agreement between these methods, and reasonable correlations with measures of atherosclerotic heart disease—such as the category specific death rates. The evidence suggests that there are regional differences in the prevalence of coronary heart disease in Scotland. However, Smith *et al* go beyond this important observation to imply that these methods can be relied upon to support the view that coronary heart disease is more prevalent in women than in men.

Data derived from the Rose questionnaire, but not from the self-reported past medical history or the coded electrocardiogram, indicated a higher prevalence of angina (particularly the milder forms) in women. Other studies consistently found a high rate of mild chest pain in women.[6] We do not know whether this difference reflects a peculiarity of the Rose questionnaire or a difference in the perception or description of chest pain between sexes.

Many physicians assume that women report a high rate of angina in response to the Rose questionnaire because the questionnaire lacks specificity and because women are describing a hypersensitivity to pain or anxiety related symptoms. But which estimate of disease prevalence is correct? Could men be underreporting their symptoms? These are important questions because there is a growing awareness that coronary heart disease in women may be misdiagnosed or undertreated and that this may account for their increased morbidity after interventions such as coronary artery surgery and angioplasty have been delayed.[7]

That at least part of the answer lies in the limitations of the Rose questionnaire or in a difference in the pain threshold of men and women in the Scottish Heart Health Study is suggested by the lack of correlation with other measures of ischaemic heart disease and the observation that women had a lower rate of more severe angina, a lower rate of ST and T wave changes and of Q wave changes, and a lower rate of ischaemic heart disease diagnosed clinically. This point needs further exploration.

As this story unfolds and we learn more about regional differences in the prevalence of ischaemic heart disease as well as differences in presentation in men and women, physicians should bear in mind that the Rose questionnaire, Minnesota coded electrocardiograms, and validated patient histories are all reasonably good survey methods. Epidemiologists should remember the major limitations of these measures when they are applied to small populations and to subgroups of a population. They should be cautious before they recommend the extrapolation of such data to policy recommendations for changes in clinical practice or in resource allocation.

Despite the bluster and noise that they may make, clinicians rely on epidemiologists for leadership. Epidemiological observations can have direct and immediate effects on the type of practice allowed or recommended for individual patients in whom atherosclerotic heart disease is suspected. The implication that physicians are systematically misdiagnosing women or any subpopulation is taken as a personal affront by most physicians. It is irresponsible for epidemiologists to present incomplete and not fully developed observations and theories because publication of such ideas in a clinical journal implies that they should be incorporated into clinical practice. In addition, there is concern that these simple tests used in population research will be forced on physicians as necessary or sufficient screening procedures for the diagnosis or treatment of individual patients with suspected coronary artery disease.

Physicians are a tolerant lot. They can probably come to terms with the knowledge that the west of Scotland has more ischaemic heart disease than the east. And as research continues into the epidemiology of coronary heart disease, they can perhaps accept the incongruous finding that young women have a higher rate of angina despite lower mortality and a lower infarction rate than young men.

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Br Heart J 1990;**64**:293–4

Editorial

Exercise and heart disease: Is there still a controversy?

Exercise enthusiasts claim prophylactic and therapeutic benefits for what they regard as an evolutionary and biologically normal, indeed essential, human activity, now largely neglected in the over-nourished West and consequently the cause of an epidemic of "loafer's heart".

The cynical, conservative view is that taking exercise is like "practising" anything else; it makes people better at performing exercise (largely from training effects on skeletal muscle), that too much exercise, like too much alcohol, is bad for you and, as with alcohol, excess means taking more than your doctor.

Cynics would also claim an equal benefit for the same amount of time spent in meditation plus dietary calorie restriction equivalent to the calories burned during exercise. They interpret statistics on the benefits of exercise as indicating that exercise adherents are a self-selected, atypical minority indulging in unnatural repetitive behaviour (proven by the small percentage of adults particularly in the United Kingdom who do take significant amounts of exercise, and the poor long term compliance achieved in most "imposed" exercise programmes).

The occasional widely reported exercise related death reinforces any excuse for physical inactivity.

Regular exercise has effects on peripheral muscle, the peripheral and central circulation, and the heart, as well as a multitude of metabolic systems and indeed psychological variables. Do we know which of these are important in terms of coronary prevention and patient management?

Measuring exercise

Unfortunately exercise is not a simple "drug" with easily measured doses, blood concentrations, and pharmacokinetics; different exercise regimens can have very variable effects. Severe anaerobic exercise for one subject may be light aerobic work for another and the biological effects will be very different. A marathon run of 26 2 miles is considered an extreme form of endurance exercise and often described as "severe exertion" but may entail only 50–65% of the runner's aerobic capacity, is run every weekend by some runners, or even by self publicists on three successive days. A series of pressups may be well within the capacity of a patient with angina or even mild heart failure who has performed an exercise ritual every day but quite impossible for a normal "fit" marathon runner not so accustomed.

Rates of walking and going upstairs or an incline vary enormously as do exercisers' abilities to judge pace or distance accurately, making self reporting of exertion unreliable and epidemiological data difficult to obtain.

Coronary prevention and exercise

Sustained aerobic exercise increases serum high density lipoprotein concentrations, with trained exercising muscle producing HDL_2-C,[1] whereas short bursts of intense exercise, such as repetitive sprints or weight training, have little or no effect on HDL concentrations. Does this mean that only aerobic exercise is beneficial in coronary prevention, or is exercise of all types better than sloth?

The benefits of exercise in heart disease prevention have been disputed and will undoubtedly remain so with some major epidemiological studies claiming a very minor role for exercise in coronary prevention compared with the established major risk factors of hyperlipidaemia, hypertension, and smoking and the benefits of exercise largely being attributed to minor changes in HDL concentrations, which in some studies could be correlated with changes in body weight.

What these studies have often neglected is the possibility that exercise may, in addition to being a less impressive independent risk factor, have effects on various factors, such as a tendency to smoke, serum lipids, body composition, blood pressure, clotting factors, and insulin sensitivity. Studies that match control and exercise groups for even some of these factors may be minimising the beneficial effects of exercise.

Exercise and "body maintenance" are often part of a lifestyle package that embodies many of the facets being promoted in coronary prevention and to the extent that exercise makes people think about their bodies—what they can do with them and how they should eat—it performs a useful promotional function. These benefits were described in a recent paper by Morris *et al*, who showed a dramatic reduction in coronary events over the subsequent nine years for civil servants who report what is termed "vigorous exercise" (> six times basal oxygen uptake) against controls and in this study a less dramatic benefit also for "fast walkers" (> 4 mph) but not for all age groups.[2] Like his previous study[3] the exercise was reported retrospectively, on this occasion for four weeks, rather than as in the previous study for three days.

Does exercise prevent progression of coronary atheroma or only the superimposed coronary events? Morris *et al* seem to favour the latter interpretation. This suggests that the beneficial effects of exercise in raising HDL concentrations, improving the lipid profile, lowering blood pressure, and increasing insulin sensitivity had no effect on atheroma progression but did affect the thrombotic and arrhythmic sequences that produce a coronary event. Is this really so or are our epidemiological techniques not sufficiently refined?

The original message from Morris's group that *vigorous* aerobic exercise was needed and that it had to be maintained on a regular basis to confer any protection (being an athlete in the past was not beneficial) is supported by the current study in which brisk walking was also preventive. The findings do not fully accord with Paffenbarger *et al*'s study which suggested an almost linear benefit from increasing caloric expenditure with lower levels of exertion being protective if sufficient time was spent on them.[4]

A study that could answer these questions is not socially possible. To recruit sufficient subjects for a randomly allocated exercise study in coronary prevention involving matched risk factors and various types of intervention with different exercise protocols followed for many years, with monitoring of diet and exertion levels in each of the groups would be an elephantine, logistic nightmare and demand severe restriction on the subjects who would only be allowed to follow their designated exercise and dietary programmes—no more or less.

Other reasons for exercise?

To exercise purely as an insurance policy against possible future coronary events is a negative way of thinking. Exercise should be a pleasure and bring its own immediate rewards. Fortunately exercise, after the initial "breaking in" period is usually enjoyable, improves the exerciser's "self image" and has a large number of other health benefits.[5] The simplest form of exercise is to walk, cycle, or jog to work and to use the stairs rather than waiting for lifts at work. Commuters who do this will benefit the environment as well as their coronary arteries. Morris has shown that his exercising group had a lower mortality from all causes. Exercise is not as dangerous as "loafing".

The first and only death in ten years in the London marathon (among 186 000 runners (average age 39) who altogether ran 5 million miles and have cumulatively run for 90 years) occurred this year. What other human activity is so safe?

Exercise as angina treatment

Todd and Ballantyne compared exercise and β blockade as treatments for angina.[6] β Blockade ameliorates angina largely by blocking the chronotropic response to exercise. Exercise training produces a sympathetic drive tachyphylaxis in which there is down regulation of β receptors and less response to chronotropic sympathetic drive after exercise training. It also increases the "efficiency" of the circulation so that a higher percentage of the cardiac output goes through the exercising muscle and the mechanical work of the heart becomes less for the same submaximal exercise load.

Todd and Ballantyne's study used a largely self-controlled short daily incremental exercise programme in a group of compliant subjects with moderately severe angina. At the end of a year the exercise group could exercise at higher load, achieved a higher heart rate before developing evidence of ischaemia, and when retested achieved a higher double product ST threshold than they had done with or without β blockade before going on the exercise programme. These improvements were not found in a non-exercising control group who if anything showed some deterioration. The success of this study, which was apparently performed without electrocardiographic monitoring for silent ischaemia but used the subjects' overt symptoms of angina to control their activities, is reassuring and suggests that in selected patients an exercise programme would be better than β blockade. The exercise group had considerably better exercise tolerance than those treated with β blockers and they felt good. We cannot predict whether fitter already active subjects in whom angina develops would derive the same benefits from exercise.

Studies in heart failure[7] and angina show the benefits of exercise, so conservative cardiologists will now perhaps accept that it is never too late to start exercise.

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ORIGINAL ARTICLES

Prevalence of coronary heart disease in Scotland: Scottish Heart Health Study

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Abstract

Data from 10 359 men and women aged 40-59 years from 22 districts in the Scottish Heart Health Study were used to describe the prevalence rates of coronary heart disease in Scotland in 1984-1986 and their relation to the geographical variation in mortality in these districts. Prevalence was measured by previous history, Rose chest pain questionnaire, and the Minnesota code of a 12 lead resting electrocardiogram. The prevalence of coronary heart disease in Scotland was high compared with studies from other countries that used the same standardised methods. A history of angina was more common in men (5·5%) than in women (3·9%), though in response to the Rose questionnaire 8·5% of women and 6·3% of men reported chest pain. A history of myocardial infarction was three times more common in men than women, as was a Q/QS pattern on the electrocardiogram. There were significant correlations between the different measures of coronary prevalence. District measures of angina correlated well with mortality from coronary heart disease, and these correlations tended to be stronger in women than in men. There was no significant correlation between mortality from coronary heart disease and measures of myocardial infarction. The study provides data on the prevalence of coronary heart disease in men and women that are valuable for the planning of cardiological services.

In Scotland mortality from coronary heart disease is very high in both sexes[1] and shows considerable geographical variation.[2] Mortality statistics are based on the cause of death given by the certifying doctor and certification practice may vary between countries. Within one country, however, the differences in the registration systems and certification patterns are smaller.[3] Incidence rates of myocardial infarction are another measure for comparing the coronary heart disease experience of different areas. A study in 1967-1968 gave some information on the incidence of myocardial infarction in Edinburgh[4] and further data are currently being collected in Glasgow as part of the World Health Organisation MONICA project.[5] This study will allow the incidence of myocardial infarction in different countries to be compared.

Another approach to assessing the extent of coronary heart disease in different countries and in different geographical areas within a country is the estimation of disease prevalence. This uses standardised methods to estimate the proportions of individuals in communities who currently have evidence of coronary heart disease. The Scottish Heart Health Study used three standard epidemiological methods to estimate the prevalence of coronary heart disease. These were the previous medical history, the Rose chest pain questionnaire, and the resting electrocardiogram coded according to the Minnesota code. We used the findings to describe the prevalences of the disease, to examine geographical variations in prevalence in Scotland, and to compare these with measures of coronary heart disease mortality. The results were compared with the prevalence of coronary heart disease found in other studies in other countries when the same methods were used.

Subjects and methods

METHODS

The measures of coronary heart disease prevalence were based on the Scottish Heart Health Study methods.[6] In this study a representative sample of men and women aged 40-59 years was drawn randomly from those registered with general practitioners in 22 different districts throughout Scotland. The target number of subjects in each district was 450 with larger numbers of participants in Edinburgh and Glasgow.

Each subject was invited to complete a questionnaire and attend a clinic for a physical examination at which a 12 lead resting electrocardiogram was recorded. The questionnaire was self-administered and included questions on past medical history of coronary heart disease and the Rose chest pain questionnaire.[7] The electrocardiograms were coded by the Minnesota method[8] by two separate coders and the results were collated by an independent arbiter.

Prevalence based on past medical history

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Table 1 Prevalence of coronary heart disease in 22 Scottish districts

	Men Median (range)	*Women* Median (range)
Past medical history (%).		
Angina	5·5 (2·7–9·1)	3·9 (1·4–7·7)
Myocardial infarction	4·3 (2·0–8·3)	1·4 (0·3–3·5)
Rose questionnaire (%):		
Any chest pain	29·1 (21·5–39·1)	24·7 (14·6–34·5)
Angina	6·3 (3·9–14·8)	8·5 (4·3–17·6)
Angina grade 1	4·2 (2·1–9·8)	6·7 (3·3–12·2)
Angina grade 2	2·1 (0·7–5·4)	2·0 (0·0–6·8)
Possible infarction	7·8 (5·3–13·1)	5·4 (2·6–8·4)
Electrocardiogram (%)		
Q/QS pattern	1·7 (0·0–5·1)	0·5 (0·0–1·7)
Ischaemic (Whitehall)	9·8 (5·4–14·1)	8·7 (5·5–15·0)
Major abnormality	5·9 (2·8–8·6)	3·8 (2·1–8·9)
Minor abnormality	10·7 (5·7–15·7)	8·0 (4·3–12·4)
Standardised mortality ratio	101 (61–136)	99 (50–147)

was measured as the percentage of subjects who had a history of angina pectoris or myocardial infarction. The Rose chest pain questionnaire identified the percentage with any chest pain, angina grade 1 and 2, and possible myocardial infarction. The electrocardiograms were used to identify individuals with a Q/QS pattern (Minnesota codes 1.1–1.2); ischaemic changes based on the Whitehall[9] categories (Minnesota codes 1.1–3, 4.1–4, 5.1–3, 7.1); and the major (Minnesota codes 4.1–2, 5.1–2, 6.1–2, 7.1, 2, 4, 8.1, 3) and minor abnormalities (Minnesota codes 1.3, 4.3, 5.3, 6.3, 9.1, 3.1–2, 2.1–2) as used in the Pooling Project[10] and other studies.

The measures of mortality from coronary heart disease were based on routine death certificate information for men and women and they were indirectly standardised for age over the range 35–64 years by standardised mortality ratios (SMR). We used the Scottish rates as the standard (the SMR for Scotland as a whole is 100), independently for men and women, and coronary heart disease was defined by International Classification of Diseases rubrics 410–414. The deaths for the years 1979–1983 were combined.

Table 3 Rank correlation between prevalence and standardised mortality ratios for coronary heart disease in 22 Scottish districts

	Rank correlation coefficient	
	Men	*Women*
Past medical history		
Angina	0·11	0·57†
Myocardial infarction	0·01	0·22
Rose questionnaire:		
Any chest pain	0·40*	0·49*
Angina	0·49*	0·77†
Angina grade 1	0·36	0·67†
Angina grade 2	0·43*	0·50†
Possible infarction	0·31	0·51†
Electrocardiogram		
Q/QS pattern	0·16	0·06
Ischaemia (Whitehall)	0·16	0·23
Major abnormality	−0·25	0·24
Minor abnormality	0·11	0·04

*0·05 > p > 0·01, †p < 0·01.

Results

There were 10 359 men and women aged 40–59 years from the 22 selected districts in the Scottish Heart Health Study. The overall response rate was 74%. Table 1 shows the range and median percentages of men and women across the districts who had positive medical histories, positive responses to the Rose questionnaire, and electrocardiographic changes.

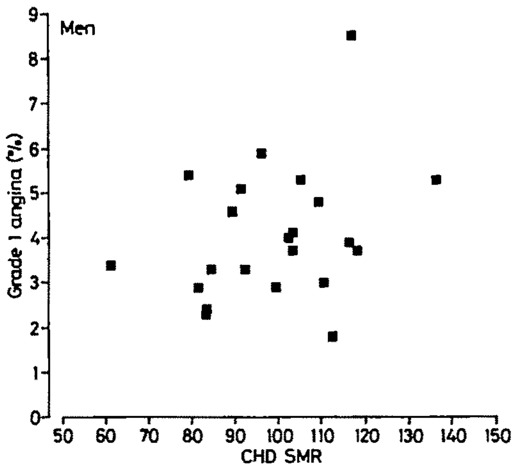
The percentage with a history of angina was slightly higher in men than in women and a history of myocardial infarction was about three times more common in men. About a quarter of men and women had at some time suffered from chest pain or discomfort but only a few conformed to the conventional Rose definition of angina.[7] The percentage of women who were positive for Rose angina was slightly higher than that of men; this difference was attributable to a difference in the less severe (grade 1) angina. A higher proportion of men than women were classified as having possible infarction according to the Rose criteria. The Q/QS pattern was three times more common in men than women but the sex differences in the other electrocardiographic groupings were not so pronounced, with the percentages in men

Table 2 Rank correlation between the different measures of the prevalence of coronary heart disease in 22 Scottish districts

	Past medical history		*Rose questionnaire*		*Electrocardiogram*	
	Angina	*MI*	*Angina*	*MI*	*Q/QS*	*Ischaemia*
			Men			
Past medical history:						
Angina	—	0·66†	0·43*	0·54†	0·26	0·50†
MI		—	0·12	0·42*	0·31	0·41*
Rose questionnaire:						
Angina grade 1			—	0·58†	0·03	0·53†
MI				—	0·19	0·40*
Electrocardiogram:						
Q/QS pattern					—	0·35
Ischaemia						—
			Women			
Past medical history:						
Angina	—	0·44*	0·73†	0·52†	0·05	0·39
MI		—	0·51†	0·32	0·33	0·44*
Rose questionnaire						
Angina grade 1			—	0·46*	0·05	0·22
MI				—	0·11	0·26
Electrocardiogram						
Q/QS pattern					—	0·28
Ischaemia						—

*0·05 > p > 0·01, †p < 0·01.
MI, myocardial infarction.

Figure 1 Rose angina (grade 1) and coronary heart disease SMR in men in 22 Scottish districts.

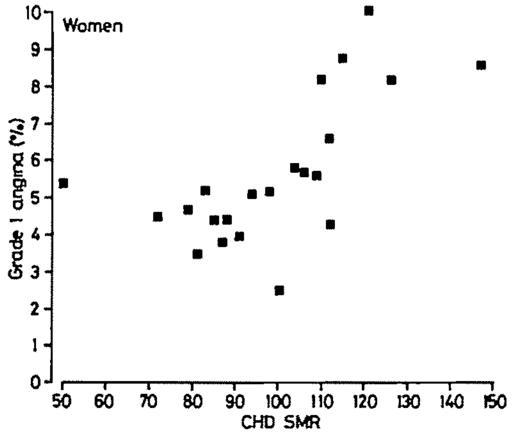


being only slightly higher than those in women.

There was a considerable range of values for all the measures of the prevalence of coronary heart disease across the districts (table 1); the range of the SMRs for coronary heart disease was also wide. The most striking differences between the sexes were in measures of myocardial infarction. Table 2 shows the interrelations between these various measures of prevalence as a matrix of rank coefficients. In men and women across the 22 districts a past medical history of angina related well to a past history of infarction, to the Rose categories, and electrocardiographic ischaemia, but not to the Q/QS pattern. A past history of myocardial infarction did not correlate well with Rose angina in men but showed a relation with other measures both in men and women. The Q/QS pattern showed some correlation with previous infarction but little relation to the other measures, while ischaemic changes correlated with most measures across the districts, with the coefficients for men being similar or greater than those for women.

Table 3 shows the rank correlation of coronary disease SMRs with the various measures of coronary prevalence in men and women across the 22 districts. The relation in women between a past history of angina and the SMR was not seen in men, and there was no relation between previous infarction and mortality. In men the percentages in a district with any chest pain, all angina, and severe grade 2 angina were all related to mortality. In women all the Rose categories correlated with mortality and the correlation coefficients were greater than those for men. Figure 1 shows the relation between grade 1 angina and coronary mortality in men and fig 2 the relation between grade 1 angina and coronary mortality in women across the 22 districts. None of the electrocardiographic groups in men or women showed any relation with mortality.

Figure 2 Rose angina (grade 1) and coronary heart disease SMR in women in 22 Scottish districts.



Discussion

Symptom questionnaires[7] were introduced in epidemiological studies because clinical questioning was shown objectively to be inconsistent and unreliable,[11] and a similar experience with interpretation of the electrocardiogram led to the development of the Minnesota code.[8] The Rose questionnaire and resting electrocardiogram are standard tests for measuring and comparing prevalence and there is extensive documentation of their sensitivity and specificity. These measures do not have to be correct in every single case but they need to be safe and acceptable for population studies, as well as being robust, repeatable, and with reasonable validity.

The findings of the Scottish Heart Health Study showed the range of values of the different measures of coronary disease prevalence across the Scottish districts. There was a considerable difference between men and women in measures of myocardial infarction but less pronounced differences in measures of angina. Few studies have included women but the Framingham study also showed that the prevalence of angina in women was more equal to that in men than was the incidence of coronary heart attacks,[12] and that women with angina had a better prognosis. The absolute values for measures of infarction were highest for the Rose possible infarction category and lowest for a Q/QS pattern. Similarly the Rose measures of angina were higher than the percentage with a previous history of angina.

Comparisons between the prevalence of coronary heart disease in the Scottish Heart Health Study and other studies must be interpreted with care despite the use of standardised methods. It is essential that the age groups are comparable because of the important effect of age on prevalence. There are two versions of the Rose chest pain questionnaire: the self-administered one may yield rates higher than the administered version—although in a recent study they were shown to be similar.[13] Electrocardiographic findings should only be compared if the grouping of Minnesota codes is identical. The original paper on the Rose self-administered questionnaire gave angina and possible infarction rates for men of 7·6% and 6·7%. These are similar to the findings in our study though the age range in the original paper was wider (40–64 years). The Whitehall study showed that 0·7% of men had a Q/QS pattern and 6·3% an electrocardiogram showing ischaemia.[14] Both these results are lower than the Scottish Heart Health Study; however, the Whitehall study used limb leads, which are less informative than chest leads.[15]

In the Pooling Project study 3% of men aged 40–59 years at entry showed major abnormalities and 9% showed minor abnormalities on the electrocardiogram[10]; both these results were lower than our findings. The Copenhagen City Heart Study reported values for major and minor electrocardiographic abnormality that were higher than we found and a comparative review reported that many countries had higher levels of minor abnormalities than Scotland and a few, including Finland, had higher levels of major abnormalities.[16] The WHO Heart Disease Prevention Project used the self-administered Rose questionnaire and found that all five countries had lower values of Rose angina than Scotland and all but Poland had lower levels of possible infarction; Q/QS changes and ischaemia patterns were less common in all countries than in Scotland.[17] However, six lead electrocardiograms were used in the WHO project and the participants were employed men. The prevalence findings of the British Regional Heart Study[18] resemble ours though the method was slightly different. More recently the Caerphilly and Speedwell surveys showed Rose angina and evidence of ischaemia on the electrocardiogram in similar proportions to those reported here but a much higher frequency of Q/QS changes (3·5–3·9%) (Minnesota 1.1–2).[19] Few studies, apart from the Copenhagen study, report findings for women. The Scottish Heart Health Study findings are very similar to the Mid-Span findings[20] for electrocardiographic abnormalities, and the results for Rose angina and a Q/QS pattern were similar to a recent Scottish study.[21]

The interrelations between the measures of prevalence used are valuable in validating each of the three methods. The previous history of angina, Rose angina, and electrocardiographic evidence of ischaemia were all closely interrelated. The Q/QS pattern showed no significant correlation with other measures probably because the number of individuals was small; however, there was a weak relation between the Q/QS pattern and a past history of an infarction in both men and women.

The positive correlations between district measures of mortality and many of the measures of disease prevalence validate the geographical variation in coronary disease within Scotland. These correlations are based on 22 districts with only two to three hundred subjects in each sex per district, which because of the low prevalence for certain presentations will tend to dilute the correlation. In general, the Rose chest pain measures of morbidity related best to mortality and the relation was stronger in women than in men despite the lower specificity of angina for coronary heart disease in women. None of the electrocardiographic measures of prevalence were related to morbidity and only possible infarction reported in the Rose questionnaire in women, of all the measures of infarction, correlated with mortality. This may be because of geographical variation in the pattern of sudden cardiac death. The Scottish Heart Health Study presented detailed information on the extent and geographical variation of risk factors for coronary heart disease.[22 23] The present paper provided data on the prevalence of coronary heart disease in both men and women which will be valuable for the planning of cardiological services.

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Transient myocardial ischaemia after acute myocardial infarction

Peter Currie, Stephen Saltissi

Abstract

The prevalence and characteristics of transient myocardial ischaemia were studied in 203 patients with recent acute myocardial infarction by both early (6·4 days) and late (38 days) ambulatory monitoring of the ST segment. Transient ST segment depression was much commoner during late (32% patients) than early (14%) monitoring. Most transient ischaemia (>85% episodes) was silent and 80% of patients had only silent episodes. During late monitoring painful ST depression was accompanied by greater ST depression and tended to occur at a higher heart rate. Late transient ischaemia showed a diurnal distribution, occurred at a higher initial heart rate, and was more often accompanied by a further increase in heart rate than early ischaemia.

Thus in the first 2 months after myocardial infarction transient ischaemia became increasingly common and more closely associated with increased myocardial oxygen demand. Because transient ischaemic episodes during early and late ambulatory monitoring have dissimilar characteristics they may also have different pathophysiologies and prognostic implications.

Current evidence suggests that important coronary artery disease frequently remains silent until the onset of a severe morbid clinical event. Thus myocardial infarction is often not preceded by angina[1] and more than 50% of patients resuscitated from out of hospital ventricular fibrillation deny previous cardiac symptoms despite angiographically demonstrated clinically significant coronary artery stenoses.[2] Recent attempts to identify and assess coronary disease have therefore focused on ways of detecting silent myocardial ischaemia as well as symptomatic episodes. Ambulatory ST segment monitoring is increasingly being used for this purpose because it is now widely accepted that any transient ST segment depression recorded reflects true myocardial ischaemia in patients with proven coronary artery disease.[3-5]

Much is currently known about the frequency, characteristics, and significance of silent myocardial ischaemia during ambulatory monitoring in patients with both stable[6] and unstable angina[7] but there is little information on patients with acute myocardial infarction. We therefore performed repeated ambulatory monitoring in 203 patients with recent acute myocardial infarction and we report the frequency and characteristics of transient myocardial ischaemia in this population.

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Patients and methods

All patients admitted to the Royal Liverpool Hospital (September 1987 to December 1988) with definite acute myocardial infarction[8] were considered eligible for the study unless they were in Killip class D, had significant valve disease, left ventricular hypertrophy, electrocardiographic conduction defects, other serious diseases, or were currently taking digitalis. Of 358 patients screened 14 refused consent, 24 died shortly after admission, and eight patients had been recruited previously. A further 109 patients were excluded because of the criteria listed above. We therefore performed ambulatory monitoring in 203 patients (152 men and 51 women, mean age 58 years (range 34–76)) with myocardial infarction.

The infarct was anterior/lateral in 93 (46%) patients, inferior/posterior in 110 (54%), non-Q wave in 47 (23%), and 36 patients (18%) were treated by thrombolysis. Forty six patients (23%) had a previous myocardial infarction, 74 (36%) had at least a 1 month history of angina pectoris, 23 (11%) were diabetic, and 114 (56%) were current smokers.

AMBULATORY ST SEGMENT MONITORING

Single channel ST segment monitoring was performed with the Oxford Medilog 4000–II. Previous studies[9] including those in our laboratory (unpublished) showed that this real time ambulatory monitoring equipment reliably measured ST segment shift both at rest and on exercise. The single modified V5 lead (CM5) predominantly used in this study was highly sensitive for detecting exercise induced myocardial ischaemia and only rarely did a second simultaneous inferior lead detect the maximum ST change.[10 11]

Ambulatory recordings were made both early (before discharge) and late (4–8 weeks after admission). Recording periods were limited to 24 hours because longer periods—for example 48 hours—are more impractical and expensive and we found only occasionally detected ischaemia not apparent on a 24 hour recording. Pre-gelled electrodes (Deva Medical) were applied and skin impedence

Table 1 Procedural details of ambulatory ST segment monitoring after myocardial infarction

Details	Ambulatory monitoring		
	Early (6·4 days) (%)	Late (38 days) (%)	p
Total patients	201	177	
Lead position			
Modified V5	185 (92)	150 (85)	
Modified V6	7 (3)	12 (7)	
CC5	4 (2)	5 (3)	
Others	5 (2)	10 (6)	
Recording ECG lead			
Q wave present	31 (15)	15 (8)	<0·04
Beseline ST elevation	38 (19)	8 (5)	<0·001
Baseline ST depression	44 (22)	19 (11)	<0·004
Drug treatment taken during monitoring			
β Blocker	71 (35)	28 (16)	<0·001
Nitrate	41 (20)	33 (19)	
Calcium antagonist	19 (9)	17 (10)	
At least one drug	102 (51)	63 (36)	<0·004

was checked (Oxford Medical Systems XI-1) to ensure a reading of less than 5 kΩ. Before each recording, patients adopted the supine, right lateral, prone, left lateral, and standing positions and underwent a period of hyperventilation (each manoeuvre for 30 seconds). ST segment shift with posture was taken into account in the analysis (see below).

Patients were given a diary to record the times of onset and finish of symptoms and daily activities and were interviewed after monitoring to ensure that all symptoms had been recorded and any discrepancies in the diaries were corrected.

ST SEGMENT ANALYSIS

The magnetic tapes (TDK AD60 cassettes) were replayed (Oxford 4500 system) to produce a report of the ST segment and heart rate trends. The ST level while the patient was supine was usually chosen as the baseline; however, if there was $\geqslant -0{\cdot}5$ mm ($-0{\cdot}05$ mV) additional ST depression from the supine level during any postural manoeuvre then the maximum ST depression during such manoeuvres was used as the baseline. Episodes of ST depression were identified on the ST trend and validated by examining, with X8 magnifying lens and a 0·1 mm graticule, electrocardiogram strips printed at each point of interest. Transient myocardial ischaemia was defined as $\geqslant 30$ s of at least $-1{\cdot}0$ mm planar/downsloping ST depression, measured at 80 ms after the J point.[12] If there was baseline ST depression of $\geqslant -0{\cdot}5$ mm, then further ($-1{\cdot}0$ mm) ST depression had to be present before ischaemia was diagnosed. Episodes of ST depression were considered to be separate if the ST shift was absent for at least 3 consecutive minutes. ST segment elevation was not used in this analysis to diagnose transient ischaemia because the diagnostic specificity of this change on ambulatory monitoring has not been well established.

Table 2 Prevalence and characteristics of transient ST depression

Variable	Ambulatory monitoring		
	Early n (%)	Late n (%)	p
Patients with STD	29/201 (14)	56/177 (32)	<0·001
STD duration (min)	1102	2731	
Total STD episodes	107	280	
STD with HR increase	40/107 (37)	211/280 (75)	<0·001
HR at STD onset (mean (SD))	82 (15)	99 (20)	<0·001
Proportion silent STD	91/107 (85)	264/280 (94)	
Symptoms in patients with STD			
All STD episodes silent	24/29 (83)	48/56 (86)	
STD sometimes symptomatic	3/29 (10)	5/56 (9)	
STD always with angina	2/29 (7)	3/56 (5)	

HR, heart rate (beats/min); STD, transient ST segment depression.

The presence or absence of a significant increase in heart rate (arbitrarily chosen as $\geqslant 10$ beats/min and resembling the figure set by other workers[3]) above the adjacent baseline in association with each episode of ST depression was determined by examining the computer derived heart rate trend. The heart rate at the onset of significant ST depression and the time of onset, associated symptoms, and daily activities during such episode were noted. Daily activities were classified as mental (for example, reading or watching television), physical (for example walking, washing, dressing, housework), exertional (for example shopping and climbing stairs or hills), resting, and sleep.

STATISTICAL ANALYSIS

We compared differences in prevalence of early and late ST depression and episodes of myocardial ischaemia associated with increased heart rate by a χ^2 test. We used the standard error of the difference between the two means to compare the heart rates at the onset of early and late ST depression and the Wilcoxon rank sum test to compare the characteristics of silent and symptomatic ischaemic episodes.

Early and late ambulatory monitoring periods were compared directly in a subgroup of patients who were taking identical medication during both recordings. The diurnal pattern of ischaemia was analysed in patients taking no antianginal drugs during ambulatory monitoring.

ETHICAL CONSIDERATIONS

The study was approved by the local ethics committee and all patients gave informed consent.

Results

BACKGROUND INFORMATION

Early ambulatory monitoring (mean 6·4 days, range 3–15) was performed in 201 patients (99%) and late recordings (38 days, range 22–93) were obtained in 177 patients (87%). Recording lasted a mean (SD) of 23·1 (2·6) and 23·5 (1·0) hours/patient respectively. Table 1 gives further details. Q waves or baseline ST segment deviation in the recording lead and concurrent β blockade were commoner during early monitoring.

TRANSIENT MYOCARDIAL ISCHAEMIA

While transient ST depression developed on late ambulatory monitoring in one third of patients, only one in seven had such changes on

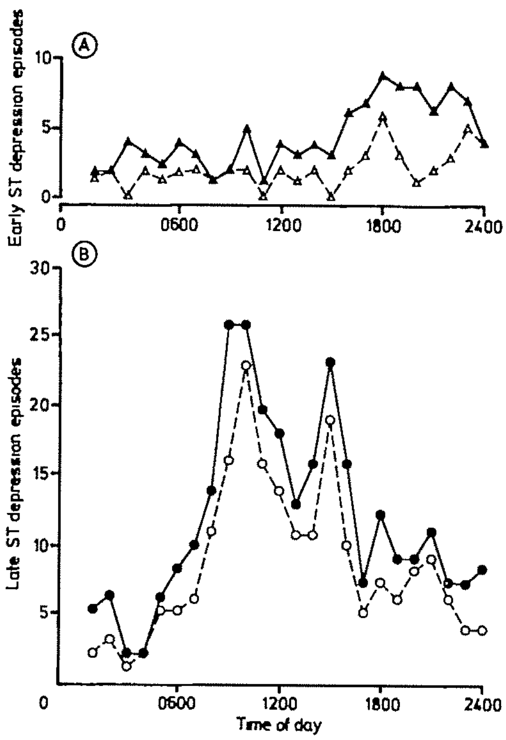

Figure 1 (A) Diurnal variation of early transient myocardial ischaemic episodes (—▲—) in patients (n = 201) undergoing ambulatory monitoring 6·4 days after acute myocardial infarction compared with episodes in patients (n = 99) taking no antianginal drugs (—△—). (B) Diurnal variation of late transient ischaemia (—●—) in patients (n = 177) undergoing ambulatory monitoring 38 days after myocardial infarction compared with episodes in patients (n = 114) taking no antianginal drugs (—○—).

early (pre-discharge) monitoring (table 2). Later episodes occurred at a higher (+25%) heart rate at onset and were much more commonly associated with periods of increased heart rate (≥10 beats/min increase) than early ST depression. These differences between early and late ischaemic episodes were also apparent in a subgroup (101 patients) taking identical antianginal drugs during both their early and late ambulatory monitoring (see later).

The pattern of late transient ischaemia showed diurnal variation with ST depression predominating during the waking hours while the pattern of early transient ischaemia was more random—though early episodes seemed to be more common in the late afternoon and evening (fig 1). Early transient myocardial ischaemia showed little diurnal change in distribution in 99 patients who were not taking antianginal drugs during early monitoring (fig 1).

Transient ischaemia was overwhelmingly asymptomatic (table 2). In fact, >80% of patients with either early or late ST depression showed only silent episodes; a further 10% of patients had both silent and symptomatic episodes and the remaining 10% experienced angina during all episodes of ST depression. The presence of absence of symptoms had no effect on the characteristics of early ST depression but during late monitoring symptomatic ST depression was greater ($p < 0·0001$) than the silent change in the ST segment ($-1·8$ (0·14) v $-1·3$ (0·02) mm, mean (SEM)) and tended to occur at a higher heart rate (105·8 (6·9) v 98·1 (1·2) beats/min, $p = 0·13$). The duration of symptomatic and silent ST depression did not differ significantly (11·5 (4·8) v 9·7 (0·9) min, $p = 0·6$).

Table 3 Daily activities during episodes of transient myocardial ischaemia

	Ambulatory monitoring	
Activity	*Early n (%)*	*Late n (%)*
Period of rest	47 (52)	71 (27)
Walking	13 (14)	54 (21)
Low-level physical activity	5 (6)	52 (20)
Mental activity	12 (13)	42 (16)
Sleeping	11 (12)	31 (12)
Exertion	2 (2)	13 (5)
Total episodes	90*	263*

*The associated activity was unknown in 17 early and 17 late episodes of ST depression.

During early monitoring most (64%) episodes of ST depression occurred at rest or during sleep, 33% during low level physical or mental activities, and only 2% during exertion (table 3). During later recordings, however, most (57%) of ST change occurred at times of low level physical or mental daily activity, 39% at rest or in sleep, and very little (5%) was related to exertion (table 3).

The maximum ST depression detected during episodes of early or late transient ischaemia (fig 2) was rarely more than $-2·0$ mm; however, a small number of episodes of ST change greater than $-3·0$ mm were recorded. Most episodes of ST depression detected on early or late monitoring lasted less than 10 minutes (81/107 episodes (76%) and 200/280 (71%) respectively) but 2–3% of episodes lasted >1 hour (maximum duration 107·5 minutes during early monitoring and 134 minutes during late monitoring).

EFFECT OF DRUG TREATMENT ON TRANSIENT ISCHAEMIA

We identified a subgroup of 101 patients who were on identical treatment during both their early and late ambulatory recordings (table 4). Two thirds (67%) of these patients were not taking antianginal drugs, 25% were on single agents, and 9% were taking a combination of treatments during the two recording periods. The characteristics of transient ischaemia in this subgroup resembled those of the study population as a whole—ST depression was more frequent during late recordings than during early recordings, there were significantly more episodes of ST depression related to an increase in heart rate during late monitoring than during early monitoring, and the mean heart rate at the onset of ST depression during late monitoring was also greater (table 4).

Furthermore, in this drug matched group, only 6 of the 12 patients with early ST depression developed any ST changes during late monitoring while 27 (82%) of the 33 patients with late ST segment depression did not show any ST shift during early monitoring.

The diurnal pattern of transient ischaemia was also examined in those patients not taking antianginal drugs during ambulatory monitoring (99 patients during early monitoring and 114 during late monitoring). Early and late monitoring in these subgroups detected 49 and 204 ischaemic episodes respectively. The diurnal distributions of these ischaemic episodes, uninfluenced by drug treatment, were similar to that of the whole study population (fig 1).

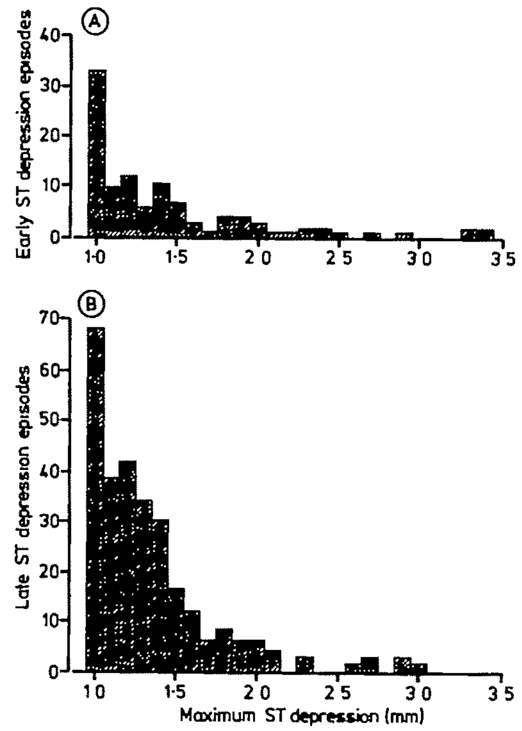

Figure 2 (A) Maximum ST depression (1 mm = 0 1 mV) during episodes of early transient myocardial ischaemia in patients (n = 201) undergoing ambulatory monitoring 6 4 days after myocardial infarction. (B) Maximum ST depression during transient ischaemia detected in patients (n = 177) undergoing ambulatory monitoring 38 days after myocardial infarction.

The relatively small number (49) of episodes of ST depression during early monitoring means that interpretation of the data remains uncertain.

Seventy one patients were taking β blockers during early ambulatory monitoring; in six late monitoring was not performed and 48 stopped taking the drug during late monitoring. In this latter group transient ST depression was commoner ($p < 0·04$) during late monitoring than during early monitoring (16/48 patients (33%) *v* 7/48 (15%)). In 17/71 patients who were taking β blockers during both recordings transient ST depression was equally common early and late (three and two patients).

INFLUENCE OF INFARCT CATEGORY, THROMBOLYTIC TREATMENT, AND DIABETES MELLITUS

The prevalence of transient myocardial ischaemia during both early and late monitoring was independent of infarct site or the presence of Q waves and was not increased in diabetic patients or in patients treated by thrombolysis.

Table 4 Ambulatory ST segment monitoring in patients taking identical treatments during early and late recordings

	Ambulatory monitoring		
Details	*Early* *n (%)*	*Late* *n (%)*	*p*
Total patients	101	101	
Treatment during monitoring:			
Single drug	25 (25)	25 (25)	
β Blocker	10 (10)	10 (10)	
Nitrate	13 (13)	13 (13)	
Calcium antagonist	2 (2)	2 (2)	
Combined drug treatment	9 (9)	9 (9)	
Two drugs	8 (8)	8 (8)	
Three drugs	1 (1)	1 (1)	
No drug treatment	67 (67)	67 (67)	
Patients with STD	12/101 (12)	33/101 (33)	0 001
Duration of STD (min)	434	1639	
Total STD episodes	40	161	
Proportion of silent STD	33/40 (83)	155/161 (96)	0 005
STD with HR increase	17/40 (43)	108/161 (67)	0 005
HR at STD onset (mean (SD))	85 (13)	100 (21)	0 001

HR, heart rate in beats/min; STD, transient ST depression.

Discussion

Silent myocardial ischaemia can cause ventricular arrhythmias,[13] sudden death,[2] or myocardial infarction[14] and may lead to cumulative impairment of left ventricular function.[15]

Recently the prevalence of silent ischaemia has been studied by ambulatory monitoring in various subgroups with coronary disease[6 16 17]; patients with recent acute myocardial infarction, however, have received little attention. Bigger *et al* detected ischaemic ST segment changes in 28% of 50 patients during ambulatory monitoring at 3 months after myocardial infarction; surprisingly, none of these episodes was symptomatic.[18] During predischarge ambulatory monitoring in 103 patients with myocardial infarction Gottlieb *et al* also detected ischaemic ST segment changes in 30 patients (29%)—mostly silent—and this group experienced a threefold increase in mortality at one year.[19] The study patients were a highly selected population, however, in whom left ventricular ejection fraction was <40%.

In the largely unselected group of patients in this study transient ST depression was present during both early and late ambulatory monitoring—though it was considerably more frequent later (33% *v* 12%). This difference probably largely reflects greater patient activity and hence greater myocardial oxygen demand during the later phase of recovery from myocardial infarction; and indeed many episodes (46%) of ST depression during late recordings were associated with some degree of physical activity whereas on the predischarge tapes 77% of such episodes occurred without any accompanying physical exertion. Some of the difference may, however, be artefactual in that the high prevalence of pre-existing and unresolved baseline ST shift (either elevation or depression) in the monitoring lead during early recordings (table 1) may have masked further significant ST depression. The timing of ambulatory monitoring after myocardial infarction may therefore be crucial. If the recording is made too early, the sensitivity of the test may be poor but if the detection of silent ischaemia after myocardial infarction is to be of prognostic value and to have a beneficial influence on treatment then monitoring cannot be delayed too long, because a high proportion of cardiac events occur in the early weeks after infarction.[20] Nearly all (90%) transient ischaemic episodes detected both in this study and in that of Bigger *et al* [18] were silent and indeed in 80% of patients showing ST depression all episodes were symptomless. Thus a greater proportion of ischaemic episodes are silent in patients shortly after myocardial infarction than in other subgroups with coronary artery disease. Although silent and painful episodes were similar in many respects, painful episodes were associated with a significantly greater degree of ST depression on recordings at 4–8 weeks after infarction.

We found a distinct pattern of diurnal variation in the incidence of transient ischaemia late after myocardial infarction which resembled that seen by others,[6 21] with most episodes occurring in the morning. This circadian cycle is likely to be related both to the known variation of plasma catecholamines[22] with corresponding changes in vasomotor tone[23] and the variation of heart rate and blood pressure[24] with accompanying increases in myocardial oxygen demand.

Interestingly ST depression on early monitoring showed little circadian variation (fig 1). The explanation of this feature is not clear but it may reflect an equalisation of myocardial oxygen demand during convalescence in hospital or possibly a loss early after infarction of diurnal variation in substances affecting coronary supply. Increased prescription of β blockers during early ambulatory monitoring may be partly responsible because others have shown a similar circadian distribution (with a tendency to afternoon and evening ischaemia) in patients with angina on drug treatment.[25] Even so, during early monitoring we did not see a morning predominance of early transient ischaemia even in patients who were not taking drugs.

In this study very few ischaemic episodes occurred during physical exertions that were vigorous enough to increase myocardial oxygen demand and cause ischaemia. This suggests that coexisting changes in coronary arterial supply may be having an effect. Perhaps at times of high coronary tone—for example in the mornings, even small increases in myocardial oxygen demand may cause ischaemia whereas the same increase in demand when coronary tone is lower may produce no ischaemia. The incidence of ischaemia as well as its temporal distribution may thus depend on the interplay between factors affecting both myocardial oxygen supply and demand. Furthermore, since early transient ST depression occurred at a lower heart rate and with less frequent increase in heart rate than that on later recordings (table 4), a reduced coronary supply early after myocardial infarction may be of greater pathophysiological importance than late changes.

The reduced occurrence of transient ST depression in patients in whom treatment with β blockers continued during late ambulatory monitoring suggests that increased myocardial oxygen demand may be important in the pathophysiology of late transient myocardial ischaemia and offers a possible explanation for the known benefits of β blockers after myocardial infarction—abolition of silent transient ischaemia.

What was the effect of concurrent drug treatment on the prevalence and characteristics of ST segment change? More patients were taking antianginal medication (especially β blockers) on early monitoring. None the less, the frequency and characteristics of early and late transient ischaemia in a subgroup taking identical treatment during both recordings (table 4) were similar to those of the population as a whole, and the overall diurnal pattern of ischaemia (fig 1) resembled that seen in patients not having drug treatment; but the number of patients studied was too small for a definite conclusion to be reached.

Our study showed that predominantly silent transient ischaemia was detected by ambulatory ST segment monitoring in a high proportion of patients shortly after acute myocardial infarction and defined its characteristics. The relation of this transient ischaemia to exercise induced ischaemia, left ventricular function, ventricular arrhythmias, and prognosis is being studied further.

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Relation between intraventricular pressure and volume in diastole

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Abstract

The pressure-volume curves for 10 patients with various types of heart disease were studied throughout mid to late diastole when both pressure and volume were increasing. The results were used to test a currently held theory that the form of this relation is exponential. It was found that for the patients examined this hypothesis was not valid.

It is widely believed that the left ventricular cavity becomes stiffer in diastole in disease. This reduced compliance is said to modify the filling pattern,[1] raise end diastolic pressure,[2] and thus limit exercise tolerance. Left ventricular compliance is measured as the rate of change of volume with pressure during the passive phase of diastole and varies throughout the filling period.[3]

It has been assumed for many years that the pressure-volume curve itself is exponential and that a rate constant can be calculated.[4] In our experience, however, the ventricular pressure-volume curve in patients with left ventricular disease can depart considerably from any simple or uniform analytical relation. To test the hypothesis that during passive filling the left ventricular pressure-volume relation can be represented without major error by an exponential we therefore examined this relation in detail with the most satisfactory methods currently available for clinical use.

Patients and methods

METHODS

We studied 10 patients, two of them on two separate occasions. The table gives their diagnoses. In all cases cardiac catheterisation was required because of standard clinical indications.

Details of patients studied

Patient	*Diagnosis*	*Sex*	*Age*
1	Congestive cardiomyopathy	F	60
2	Mild mitral stenosis with regurgitation	M	27
3	Coronary artery disease	M	60
4	Coronary artery disease with left ventricular dysfunction	M	46
5	Coronary artery disease	M	55
6	Coronary artery disease	M	45
7	Coronary artery disease	M	70
8(a)	Coronary artery disease	M	47
8(b)	Coronary artery disease with induced angina	M	47
9(a)	Coronary artery disease	M	57
9(b)	Coronary artery disease with induced angina	M	57
10	Aortic valve dysfunction with LV hypertrophy	F	68

Biplane cineangiograms were performed during held mid-inspiration (60° left and 30° right anterior oblique projections) at a frame rate of 50/s with 50 ml of Urografin 370 at a flow rate of 12 ml/s injected into the ventricle. The left ventriculograms were calibrated by displacing the catheter table by 10 cm.

Ventricular pressure was measured by a Gaeltec tip micromanometer mounted on the angiographic catheter with atmospheric pressure as zero. The micromanometer was immersed in saline for 20 minutes before use to minimise zero drift, which was found to have been less than 2 mm Hg by the end of the study for all patients. The transducer was calibrated in situ against peak systolic and minimum diastolic pressure recorded through the angiographic lumen. Pressures were recorded photographically at a paper speed of 0·1 m/s with a simultaneous electrocardiogram.

ANALYSIS OF DATA

The beats we analysed occurred within the first five after the start of contrast injection, when the haemodynamic effects of the agent itself are negligible, and were not extrasystolic or postextrasystolic. The onset of the QRS complex of the electrocardiogram was used to gate a light emitting diode and thus identify its timing on the cine film. The cineangiograms were digitised in both planes frame by frame[5] throughout the cycle being studied. The timing of mitral opening was taken as the first appearance of unopacified blood through the mitral valve at the start of diastole. This was best identified on the right anterior oblique projection. Cavity volume was derived for each pair of right anterior oblique and left anterior oblique frames by computer reconstruction of the cavity.[6] The two frames were aligned at the apical point, taken as the point furthest from the mid-point of the aortic root on each. The right anterior oblique view was then sliced at 50 levels perpendicular to the mid-aortic to apical line, thus providing 100 points to define the outline of the cavity. These points were then projected across to the left anterior oblique view and the intersections with its periphery were recorded. We used computer aided surface fitting techniques to reconstruct the three dimensional cavity shape and measure its enclosed volume. This method has previously been validated directly against plaster casts of left[6] and right[7] ventricles. Figure 1 shows some of the ventricular cavity shapes for patients in this study.

The period of passive left ventricular filling was taken as starting at the time when pres-

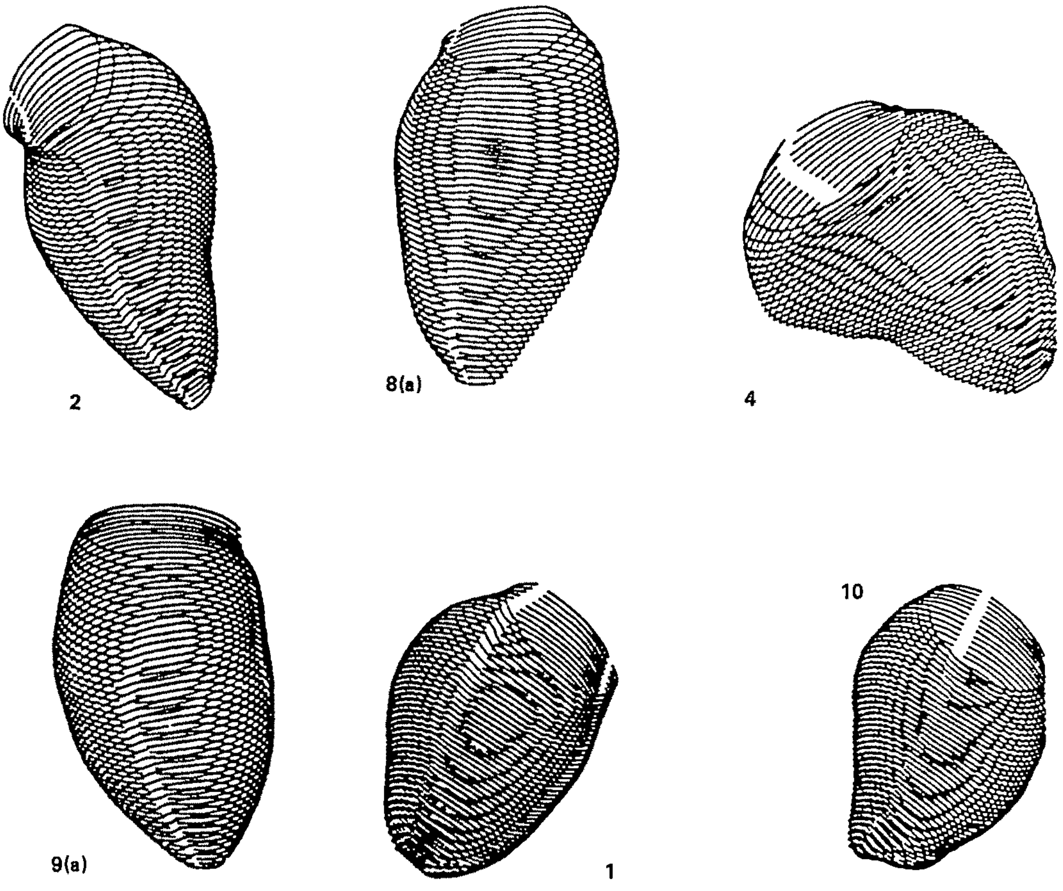


Figure 1 Typical computer aided reconstructions of the left ventricular chamber for six of the patients studied.

sure and volume started to increase simultaneously at the end of rapid filling. We chose this as a practical definition and cannot exclude the possibility of some residual tension for a short time afterwards. This contrasts with the period of rapid filling when pressure falls as volume increases. The end of passive diastole was identified as the onset of the sudden increase in filling rate associated with left atrial systole. This procedure required analysis of 5–11 frames per patient.

From this information we examined the relation between pressure and volume by regression analysis, using linear (P against V) and semilogarithmic (ln P against V) plots. For each we calculated the correlation coefficient, the slope and intercepts along with their standard errors, and the standard error of the estimate. We took atmospheric pressure as zero in the semilogarithmic analysis. In line with current reported practice we did not investigate the effect of allowing the assumed zero value for pressure measurement to vary in order to improve agreement. We also examined the plot of pressure against dP/dV (the ventricular or cavity stiffness). If the relation between pressure and volume is exponential there should be a simple linear relation between pressure and dP/dV, with both increasing as filling proceeds. We studied the nature of the relation in individual patients, with particular reference to its form. We noted whether dP/dV increased uniformly throughout passive filling or whether it showed points of inflection, remaining constant or even falling as pressure rose.

Results

PRESSURE-VOLUME RELATIONS

Figure 2 shows the pressure-volume curves during passive filling for individual patients. Their shape varies greatly. Approximately half the patients showed some increase in slope towards the end of passive diastole but this was by no means uniform.

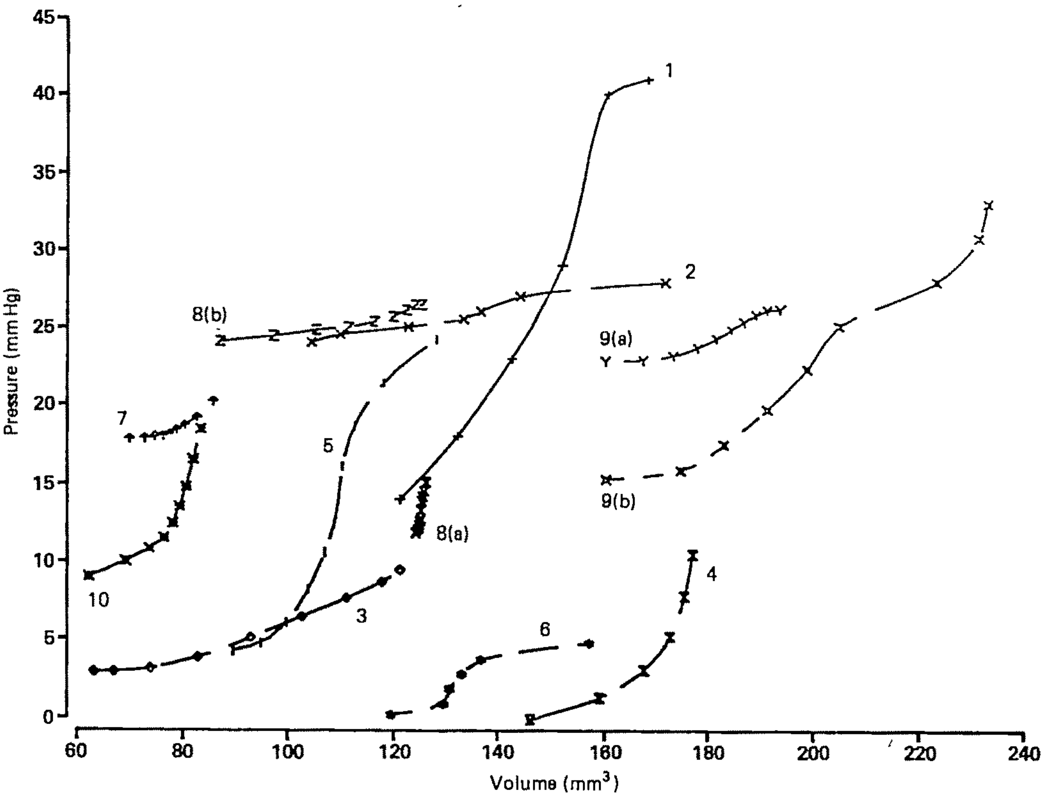
REGRESSION ANALYIS

Correlation coefficients for linear analysis of pressure against volume varied between 0·89 and 0·98. For semilogarithmic analysis they varied between 0·83 and 0 99. There was no significant difference between values derived from the two approaches when individual values were compared. The standard error of estimated volume derived from pressure meaurements was 3·7 (1·9) mm Hg when logarithmic analysis was used and 4·0 (1·6) mm Hg with linear analysis. Again there was no significant difference between these values.

PRESSURE-CAVITY STIFFNESS RELATION

Figure 3 shows curves from individual patients. A progressive increase in cavity stiffness (not necessarily linear) with pressure was seen in only four. In the remainder the curve was sigmoid with stiffness falling rather than rising for at least part of the period of pressure rise.

Figure 2 Portions of pressure-volume curves for all 12 studies. Pressure and volume were both rising in diastole.



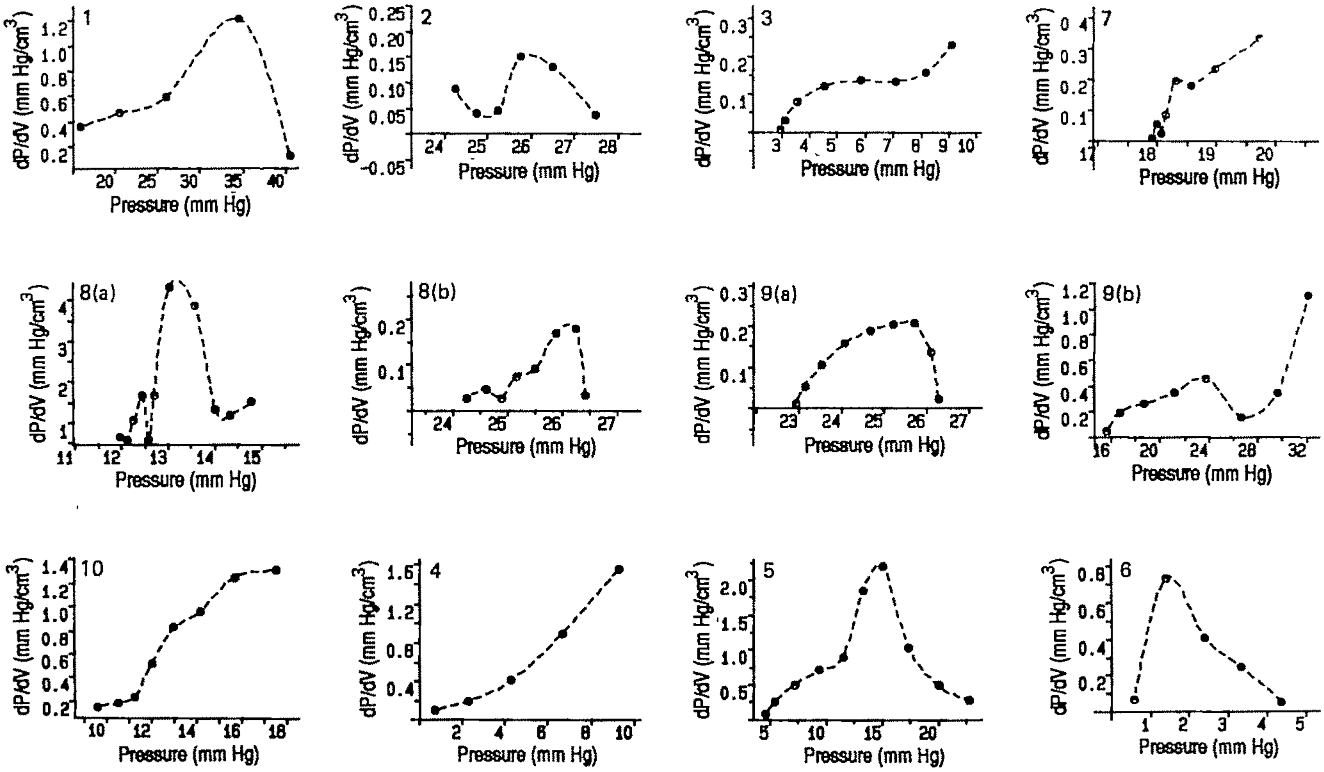


Figure 3 Plots of dP/dV against P for each patient.

Discussion

The stiffness of the left ventricular cavity during the passive phase of diastole is estimated from its pressure-volume relations. The curve of pressure against volume is often not linear, with the slope increasing towards end diastole. It has therefore become traditional, since the original studies of Noble *et al*,[4] to use an exponential analysis and plot the logarithm of pressure against volume. This approach has affected the way in which diastolic function is understood. Unlike other mathematical functions exponential analysis allows a rate constant to be calculated; in the present context it is usually referred to as a stiffness constant and used by some to express ventricular stiffness itself. Departures of the curve from the assumed exponential have been taken as evidence that some additional mechanism is influencing pressure-volume relations; the presence and even the magnitudes of viscous forces have been calculated on this basis by Eichhorn *et al.*[8]

We undertook the present study because we were impressed by how often the pressure-volume relations in patients with left ventricular disease departed from any simple or uniform relation. We deliberately excluded the rapid filling period and also atrial systole from consideration, when other mechanisms might have been acting and when viscous effects could be invoked. The methods we used were the most satisfactory available clinically and our approach to volume estimation, in particular, was not subject to limitations imposed by single plane angiography or assumed geometry. In common with virtually all other studies, we measured ventricular pressure at only one site within the ventricle, a questionable procedure if intraventricular pressure differences develop within the cavity. Such differences would be expected at times of rapid filling and indeed have been documented. During the passive phase of diastole, however, the filling rate is slow, and there is no theoretical or experimental reason to believe that they are present. Our results clearly showed that the relation between pressure and cavity stiffness departed very significantly from the assumed exponential. Even the undemanding criterion that ventricular stiffness should increase, not necessarily linearly, with pressure was met in only one third of the patients. In eight, calculated cavity stiffness actually fell with increasing pressure over part of the period being examined. We conclude that critical examination in patients with left ventricular disease showed that this exponential analysis was of very limited value.

Influences external to the left ventricle may have distorted our results, thus causing the underlying exponential to be obscured. It has been suggested that measured cavity stiffness might be modified by pericardial restraint.[9] While this undoubtedly occurs in a few patients after open heart surgery,[10] we do not feel that it was important in our patients. Pericardial restraint is an end diastolic phenomenon, occurring only late in ventricular filling. It would therefore appear as a sudden increase in calculated stiffness. We found no evidence of this: indeed in six of our patients stiffness was actually falling in the cine frames before the onset of atrial systole. In addition, all our patients showed a further volume increase with atrial contraction that would be out of the question if the ventricle were restrained by a structure as unyielding as the pericardium. Right ventricular disease has also been invoked as a possible mechanism influencing left ventricular pressure-volume relations. Again, we consider this to have been unlikely in our patients most of whom had dominantly left ventricular disease. The influence of the right ventricle is mediated largely through the pericardium[11]; any more direct action is associated with distortion of the left ventricle which was not present. We may have been incorrect to take atmospheric as the zero for pressure measurement, though this has been assumed in all previous studies. During isovolumic relaxation, however, the observed time course of the declining pressure can be made to agree more closely with an assumed exponential if the asymptote as well as the time constant is allowed to vary.[12] In normal subjects the effective zero for pressure measurement during this period has been found to be large and negative, often as much as 50–60 mm Hg below atmospheric. We do not think that manipulating asymptotes in this way would have improved agreement during the passive phase of diastole. The only way in which it could have done so in the patients in whom stiffness was declining towards end diastole was for the effective zero to have actually risen above the value actually measured in the ventricle, a suggestion not worthy of being considered further.

It does, however, bring to light a possible paradox. How can the large negative asymptote during isovolumic relaxation suggested by exponential analysis be reconciled with the assumed atmospheric one during filling? Is one or other incorrect or has there been a change? If the latter is true, what is the time course of this change and how does it affect predictions about "incomplete relaxation" that depend on extrapolation of the exponential curve derived during isovolumic relaxation into the period of filling?[13] Clearly there are major inconsistencies between the two sets of results that in our opinion merely underline the unsatisfactory nature of both.

Our results emphasise the complex nature of diastolic left ventricular pressure-volume relations. Even if the isolated left ventricular pressure-volume curve is exponential when heart function is normal there is every reason to suppose that it departs from this in the intact patient with disease. Ventricular involvement is frequently non-uniform, particularly in coronary artery disease, whereas hypertrophy leads to major structural abnormalities. Even in the normal heart the structure of the myocardium is very highly organised with fibre angle varying across the wall and in different regions of the ventricle. Changes in transverse dimension are mediated more by myocardial thickening or thinning than by changes in fibre length.[14]

We are dealing with a thick-walled pressure vessel with a complex wall structure that is highly orthotropic in nature. The rate of volume change with pressure will depend not only on the geometry but also on the stiffness of the material of the myocardium. This material stiffness itself may not be constant but could well vary with time and thus with volume, possibly in some non-linear way. With this in mind it is not surprising that the pressure-volume relation in diastole does not follow a simple exponential law. Relaxation may even persist, to some degree, beyond the period of rapid filling into the period that we have considered. Indeed we found that myocardial stiffness did vary during passive filling and our findings in this respect will be described in a future paper. Thus the diversity of passive diastolic relations seen in a small number of patients with heart disease is not surprising. We suggest that this diversity be accepted and if possible analysed rather than effectively suppressed by procrustean assumptions. Exponential analysis has not contributed significantly to an understanding of left ventricular diastolic behaviour and we suggest that it be abandoned.

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The limited potential of special ambulance services in the management of cardiac arrest

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Abstract

For six months a survey was made of all the patients in the Nottingham District Health Authority who died or who were brought to hospital after a cardiac arrest outside hospital. During this period just under half of the emergency ambulance shifts were covered by specially trained crews with defibrillators. During the study period the ICD coding of death certificates indicated that 894 (25%) of the 3575 deaths were due to ischaemic heart disease. During this period the ambulance service received 17 749 emergency calls, which included 445 patients who had cardiac arrests outside hospital. One hundred and forty seven of these patients were carried by ambulances equipped with defibrillators and resuscitation was attempted in 83. Seven patients survived to leave hospital.

The special ambulance service was cost effective—a simple calculation suggests that the cost per life saved was approximately £2600, but it seems unlikely that special ambulance services will materially affect community fatality rates from ischaemic heart disease.

Special ambulance services for the transport and treatment of patients with a cardiac arrest have been in operation in the United Kingdom for more than twenty years. Different approaches have been used[1-4] but widespread acceptance of the need to extend the skills of ambulance personnel has not been accompanied by equally widespread attempts to investigate either the effectiveness of ambulance personnel with advanced training or the overall potential benefit to the community. The benefit to an individual who is successfully resuscitated from cardiac arrest is obvious[5] and perhaps because of this it has been suggested that community mortality from ischaemic heart disease may be significantly reduced by the introduction of resuscitation by paramedical services.[6]

In 1983 the Nottinghamshire Ambulance Service began advanced training in resuscitation skills for ambulance personnel on the accident and emergency shifts. We have described elsewhere both the training programme and the results from the first 403 cardiac arrests suffered outside hospital in the county of Nottinghamshire and attended by our crews.[7 8] Now that nearly half of our emergency ambulance shifts have crews with advanced training we decided to investigate the extent to which our ambulance service is involved with deaths and cardiac arrests that occur outside hospital so that we could estimate the potential of our new service for saving lives.

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Patients and methods

METHODS

We reviewed all the patients who suffered a cardiac arrest outside hospital and for whom an emergency ambulance was summoned. Some of these patients were found dead and had clearly been dead for some time, while others were seen to collapse or were found in circumstances that suggested that cardiac arrest had occurred recently. We excluded those patients with a death certificate issued by a general practitioner.

The Nottingham District Health Authority serves a population of 617 000 and there is a single accident and emergency department at University Hospital to which ambulances bring all those who suffer a cardiac arrest outside hospital. During the six month period 1 January to 30 June 1988 the records of the accident and emergency department were inspected daily to identify the patients who had been certified dead on arrival at hospital or who had died after admission to hospital after a cardiac arrest. Such deaths are usually reported to the coroner and the cause of death was identified from coroner's records. We excluded patients found to have died of causes other than coronary disease.

Death certificate returns to the district health authority from registrars of births, deaths, and marriages for this six month period were inspected to identify the number of deaths within the area. Death certificate entries were coded according to the 9th revision of the *International Classification of Diseases* to identify the deaths that were attributed to ischaemic heart disease (ICD codes 410-414).

All patients who had been carried on an ambulance equipped with a defibrillator by a trained crew were identified from records submitted to one of us (JMR) by the ambulance personnel. These records were completed for all patients in whom resuscitation had been attempted, whether successful or not. Crews were also encouraged to complete forms to identify patients who had been certified dead on arrival without any attempt at resuscitation. Any patient who was successfully resuscitated and admitted to hospital was followed until death or hospital discharge.

To simplify comparison with data from death registration this investigation was confined to cardiac arrests managed by ambulance crews based at the eight ambulance stations within the Nottingham District Health Authority, though records are maintained of all cardiac arrests managed by specially trained crews throughout the county of Nottinghamshire.[8]

The records of the Nottingham ambulance stations were analysed to identify the proportion of accident and emergency shifts for which a defibrillator and a trained crew were available. The working day of the emergency ambulance service is divided into a variable number of shifts and a variable number of ambulances are available at different times of the day and on different days of the week. For the purposes of this study, therefore, an "ambulance shift" was defined as the usual work period of an individual ambulance manned by two people.

Results

For the six month period from 1 January 1988 to 30 June 1988 3575 deaths were reported within the Nottingham District Health Authority; on the basis of the death certificates (mainly issued by general practitioners) 894 (25%) of these deaths were coded as being due to ischaemic heart disease. The ambulance service as a whole received 17 749 emergency calls during this period and transported to University Hospital 445 patients who suffered cardiorespiratory arrest outside hospital.

Figure 1 summarises the overall pattern of deaths within the community and the involvement of the ambulance service. The study period was covered by a total of 5736 emergency ambulance shifts, 2760 (46.5%) of which were worked by a crew trained and equipped to use a defibrillator. Of the 445 victims of cardiac arrest brought to the accident and emergency department 298 (67%) were transported by crews who had not been trained in defibrillation and these patients were either certified dead on arrival or after a period of attempted resuscitation in the accident department. No patient survived who had a cardiac arrest outside hospital and who was transported by a crew without special training or a defibrillator. One hundred and forty seven patients (33% of those with a cardiac arrest) were brought to hospital by a crew able to attempt defibrillation: in 64 of these patients no attempt at resuscitation had been made and they were certified dead on arrival at hospital; an attempt had been made by the ambulance crew to resuscitate 83 patients.

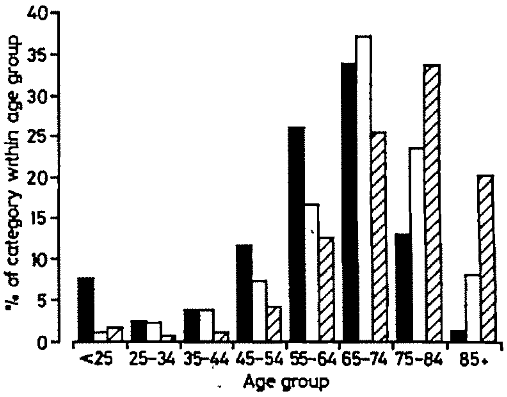


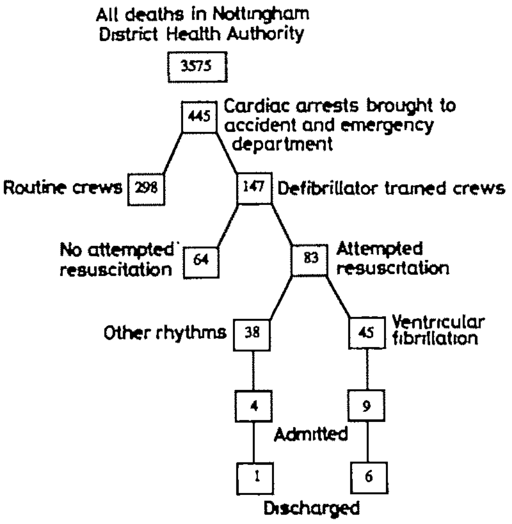
Figure 2 Age structure of the group of 83 patients in whom resuscitation was attempted (black bars), of the 64 patients who were brought to hospital by special crews without resuscitation attempt (open bars), and of the 3575 patients who died in the Nottingham District Health Authority during the study period (hatched bars).

Ventricular fibrillation was the observed cause of the cardiac arrest in 45 (54%) of the 83 patients in whom resuscitation was attempted and defibrillating shocks administered. Nine of these patients were admitted to the coronary care unit and six were discharged alive. Four patients resuscitated from cardiac arrest due to rhythms other than ventricular fibrillation were admitted but only one of these survived.

Figure 2 shows the age distribution of the patients who died in the Nottingham District Health Authority during the study period. The median age of death for the whole group was 76. The median age of patients transported to hospital by ambulance without any attempt at resuscitation was 70 but the median age at death in the group in which resuscitation was attempted by a trained crew was 64.

Figure 3 shows the cumulative percentage of response times in the 17 749 emergency calls

Figure 1 Management and outcome of patients with cardiac arrests outside hospital in the Nottingham District Health Authority during a 6 month period.


All deaths in Nottingham District Health Authority
3575
445
Cardiac arrests brought to accident and emergency department
Routine crews
298
147
Defibrillator trained crews
No attempted resuscitation
64
83
Attempted resuscitation
Other rhythms
38
45
Ventricular fibrillation
4
9
Admitted
1
6
Discharged

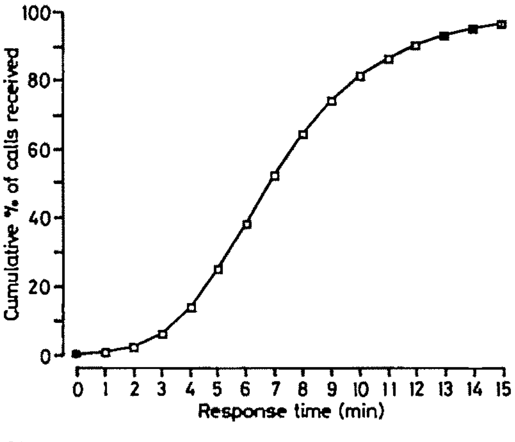


Figure 3 Cumulative frequency (%) of time intervals from the call for an emergency ambulance to its arrival at the patient.

for an ambulance during the study period. The median response time was 7 minutes, and was the same for all types of emergency ambulance, whether or not they had a specially trained crew.

Discussion

This survey was conducted during the first half of 1988, and at that time our extended training scheme for ambulance personnel had been in operation for five and a half years. We had trained sufficient crews for nearly half of the emergency ambulance shifts to have specially trained crews equipped with defibrillators. Only 12.6% of the total deaths in the community involved a call to the ambulance service, though ambulances were involved in half of the deaths due to ischaemic heart disease.

Although half of the ambulance shifts were covered by special crews, such personnel attended only one third of the patients who died. The cause of this discrepancy is not clear, but it may reflect information given to the ambulance controllers. The controllers had no specific protocol for selecting a routine emergency ambulance or one equipped with a defibrillator for response to a particular type of call; they used their judgment. It seems likely that when a call was received concerning a patient who had been found dead and who had probably been dead for some time a routine ambulance was dispatched. Such patients are probably more common than those seen to collapse, so routine vehicles may well have carried a higher proportion of patients who fall within our definition of "cardiac arrest".

Even if all our emergency ambulances had specially trained crews with defibrillators, it is clear that there would be little impact on community fatality rates from heart attacks and that previously published estimates of the effect of such services[6] have been over-optimistic. Many of the patients described as having a cardiac arrest outside hospital might be better described as "found dead". Our specially trained crews, who might be expected to be enthusiastic about resuscitation, only attempted this in just over half the patients they attended with cardiac arrest; in the remainder a resuscitation attempt was clearly too late. The use of automatic defibrillators could reduce training time and thus increase the number of trained crews, but there is no reason to suppose that the proportion of successful resuscitations would increase. If we make the optimistic assumption that complete cover of our emergency ambulance service with defibrillator equipped ambulances would be associated with the same rate of attempted and successful resuscitation demonstrated by the crews we have at present, then we can calculate that in our population of 617 000 at best between 30 and 40 lives would be saved in a full year. While this saving of lives is vital to the individuals who benefit it must be seen in the context of nearly 2000 deaths each year from coronary disease, and a total of over 7000 deaths in our community.

There are many ways in which it might be possible slightly to improve the number of survivors of cardiac arrest outside hospital but few have been critically evaluated. In some communities it might be more appropriate for general practitioners to have their own defibrillators[9] but this will only help where patients tend in the first instance to call their general practitioner rather than the emergency services. It might be possible to educate potential patients to call for help more quickly or to call the emergency ambulance service rather than their general practitioner, though our experience of this has had only limited success.[10] It seems unlikely that our median ambulance response time of 7 minutes can be much improved, but it might be useful to concentrate special ambulance services where there are large crowds.[11]

Public education programmes in cardiopulmonary resuscitation may lead to a higher proportion of resuscitation attempts by special ambulance services having a successful outcome.[12] The presence of a doctor on the emergency vehicle should improve the success rate of a resuscitation, but when we compared an ambulance manned by a doctor with an ambulance with a specially trained crew the results were very similar.[13] Further extension of the skills of the ambulance crew to include intubation and intravenous fluid and drug administration[14] may lead to a higher proportion of successful resuscitations but training of all emergency crews to this standard will take several years. It is also difficult to evaluate the effects of skills other than defibrillation. While any or all of these measures might save a few extra lives it seems unlikely that they will make a significant impact on community mortality.

We made a simple estimate of the cost of saving lives with our special ambulance service by adding the salaries of the staff required for the service to the cost of purchasing and maintaining equipment. The staff required include a training officer and one additional trained ambulance crew to allow for the time needed for training. The ten defibrillators provided mainly from charitable sources for the Nottingham-based crews cost £4500 each. If we assume that the present rate of discharge from hospital is maintained over a seven year period (the projected life of the defibrillators) then with our present level of staffing 84 patients will be discharged from hospital at a cost of £45 000 for defibrillators plus £23 000 for their maintenance and approximately £150 000 for the salaries of the training officer and the additional ambulance staff. The cost per life saved is therefore approximately £2600—this calculation takes no account of the quality of life of the survivors nor of the balance of costs and benefits in terms of loss of income and taxes or the payment of social benefits. In simple terms, however, our advanced training scheme for ambulance crews seems to be highly cost effective.

We thank our ambulance crews and their controllers for their cooperation and the staff in the accident and emergency department and the coronary care unit of University Hospital, Nottingham, who contributed to the success of this project. The research aspects of this study were supported by a grant from the Department of Health and Social Security.

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Novel exercise protocol suitable for use on a treadmill or a bicycle ergometer

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Abstract

Many exercise protocols are in use in clinical cardiology, but no single test is applicable to the wide range of patients' exercise capacity. A new protocol was devised that starts at a low workload and increases by 15% of the previous workload every minute. This is the first protocol to be based on exponential rather than linear increments in workload. The new protocol (standardised exponential exercise protocol, STEEP) is suitable for use on either a treadmill or a bicycle ergometer. This protocol was compared with standard protocols in 30 healthy male volunteers, each of whom performed four exercise tests: the STEEP treadmill and bicycle protocols, a modified Bruce treadmill protocol, and a 20 W/min bicycle protocol. During the two STEEP tests the subjects' oxygen consumption rose gradually and exponentially and there was close agreement between the bicycle and the treadmill protocols. A higher proportion of subjects completed the treadmill than the bicycle protocol. Submaximal heart rates were slightly higher during the bicycle test. The STEEP protocol took less time than the modified Bruce treadmill protocol, which tended to produce plateaux in oxygen consumption during the early stages. The 20 W/min bicycle protocol does not take account of subjects' body weight and consequently produced large intersubject variability in oxygen consumption.

The STEEP protocol can be used on either a treadmill or a bicycle ergometer and it should be suitable for a wide range of patients.

Many different exercise protocols are used in clinical cardiology. Because no single test is suited to the wide range of patients' exercise capacities many centres use two protocols—one for fitter patients and another for more limited patients. This, however, requires a pre-test estimate of exercise capacity, which is not always accurate.

Several features are desirable in any exercise protocol. It should be applicable to a wide range of patients so that assumptions about exercise capacity do not have to be made before the test. The most severely limited patients should be able to exercise for at least 3 minutes,[1] which necessitates starting at a low workload. On the other hand, the test must not be too long or fatigue and boredom (of both the patient and supervising physician) may become limiting factors. An average duration of 10 minutes has been suggested,[2 3] and all patients should reach their maximum by 15 minutes.[2]

A further complication is that various exercise laboratories use different modes of exercise testing: bicycle ergometers predominate in mainland Europe while treadmills are favoured in the United Kingdom and United States. These two modes of exercise have an essential difference: on a treadmill the work performed during each stage is dependent on body weight, while bicycle exercise is weight independent. Bicycle exercise testing therefore needs to be standardised for body weight so that different subjects perform similar relative work at each stage, otherwise larger subjects will have a performance advantage. Most existing bicycle protocols fail to take this into account. During treadmill exercise the patient has to carry his or her own weight and so this mode of exercise testing is automatically standardised.

The aim of this study was to devise a new protocol that would accommodate the full range of patients' exercise capacity and could be used on either a treadmill or a bicycle ergometer.

Subjects and methods

The cardiopulmonary responses to the new exercise test were compared with standard protocols in 30 healthy male volunteers (mean age 38 years (range 28–55); mean weight 74 kg (range 57–97)).

EXERCISE PROTOCOLS

The new protocol was designed to begin at a low workload (2 METS, 7 ml/kg/min) and the initial increments were kept small by increasing the workload by 15% of the previous stage every minute. This results in an exponential rise in workload, and the highest stage required to test even relatively fit patients is reached after 15 minutes. This is the first protocol to be based on exponential rather than linear increments in workload.

The mathematical model of this new exercise test was translated into a treadmill protocol by means of standard formulas for oxygen consumption derived from treadmill speed and gradient.[4] At each stage either the treadmill speed or the gradient was increased, never both together. Table 1 shows the resulting STEEP treadmill protocol.

The STEEP test was applied to a bicycle

ergometer after allowing for body weight. Table 2 was derived, again by means of standard formulas,[4] to predict the bicycle protocol required to elicit the same relative oxygen consumption as the treadmill protocol for a given body weight (rounded to the nearest 5 kg).

METHODS

Each of the 30 men performed four exercise tests in random order on separate visits at the same time of day in the postabsorptive state. They exercised to symptom limited maximum on a modified Bruce treadmill protocol[5] and a 20W/min bicycle protocol.[6] They exercised either to exhaustion or to completion of the 15 minute treadmill and bicycle STEEP protocols. All tests were performed in an air conditioned exercise laboratory at a constant temperature.

A Marquette MAC 2 was used for the treadmill tests and a Bosch ERG 551 electronically braked ergometer was used for the bicycle protocols. Respiratory variables were determined during exercise by an automated gas analysis system (Beckman metabolic measurement cart; classic exercise model system 2) that was calibrated for barometric pressure. Before each test the oxygen and carbon dioxide sensors were calibrated with a standard gas mixture containing 16% oxygen, 4% carbon dioxide, and 80% nitrogen.

The oxygen consumption ($\dot{V}O_2$) for each stage of the various protocols was taken as the average over the last 30 seconds of that stage. Heart rate was taken from the electrocardiogram during the last 10 seconds of each stage. Systolic blood pressure was determined by palpation every 3 minutes.

STATISTICAL ANALYSIS

The significance of differences in the mean heart rate, $\dot{V}O_2$, and blood pressure between the protocols was determined at each stage by uncorrected paired *t* tests. The significance after Bonferroni correction for multiple comparisons is also discussed in the text. Repeated measures analysis of variance was not applied because the subjects stopped exercise at different rates on the various protocols; this led to missing data which were "not at random". The significance of differences between the proportions of subjects failing to complete the two STEEP tests was assessed by McNemar's test for comparing correlated proportions.

Results

AGREEMENT BETWEEN THE TWO STEEP TESTS

Twenty seven men completed the 15 minute STEEP treadmill test and 18 completed the bicycle protocol ($p < 0.005$). Figure 1 shows the oxygen consumption during each stage of the two STEEP tests. During both the treadmill and bicycle protocols the subjects' $\dot{V}O_2$ rose in an exponential manner. There was no significant difference in mean $\dot{V}O_2$ for 11 of the 15 stages. The subjects' oxygen consumption was slightly, but statistically significantly, higher for the first three minutes and the final minute of the treadmill test (fig 1). None of the differences was significant after correction for multiple comparisons.

Figure 2 shows the subjects' heart rates during the two STEEP tests. Heart rates were significantly higher during the middle stages of the bicycle test, but the difference was less than 10 beats per minute at every stage. There was no significant difference in blood pressure between the two modes of exercise.

COMPARISON WITH EXISTING PROTOCOLS

Figure 3 compares oxygen consumption during the STEEP treadmill protocol with that during the modified Bruce protocol. The modified Bruce protocol required 19 minutes to complete the range of workloads covered by the STEEP test in 15 minutes. A plateau in $\dot{V}O_2$ was achieved during the first four stages of the

Table 1 STEEP treadmill protocol

	Stage (min):														
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*
Speed (mph)	1·5	2·0	2·0	2·0	2·5	2·5	2·5	3·0	3·0	3·0	3·5	3·5	3·5	4·2	5·0
Speed (km/h)	2·4	3·2	3·2	3·2	4·0	4·0	4·0	4·8	4·8	4·8	5·6	5·6	5·6	6·7	8·0
Elevation (%)	0	0	1·5	3	3	5	7	7	9	11	11	13	16	16	16

Table 2 STEEP bicycle protocol showing the workload for each of the 15 stages of the protocol as determined by the subject's body weight in kilograms

	Stage (min):														
Weight (kg)	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*
50	15	20	25	30	40	50	60	70	85	95	110	125	145	170	185
55	15	20	30	35	45	55	65	80	95	105	125	140	160	185	205
60	15	25	30	40	45	60	70	85	100	115	135	150	175	200	225
65	20	25	35	40	50	65	80	90	110	125	145	165	190	220	240
70	20	25	35	45	55	70	85	100	120	135	155	175	205	235	260
75	20	30	40	45	60	75	90	105	125	145	170	190	220	250	280
80	25	30	40	50	65	80	95	115	135	155	180	200	235	270	295
85	25	35	45	55	65	85	100	120	145	165	190	215	250	285	315
90	25	35	45	55	70	90	105	130	150	175	200	225	265	300	335
95	25	35	50	60	75	95	115	135	160	180	215	240	280	320	350
100	30	40	50	65	80	100	120	140	170	190	225	250	295	335	370

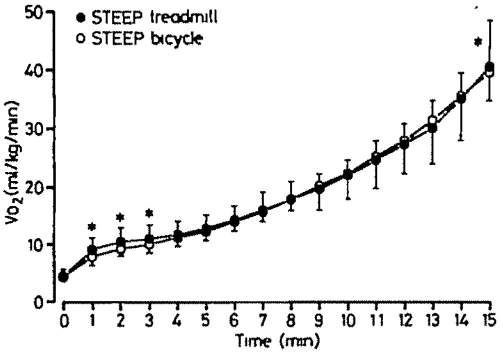

*Figure 1 Mean (SD) oxygen consumption of 30 healthy men performing the two STEEP protocols. $\dot{V}O_2$, oxygen consumption. *$p < 0.05$ on uncorrected t test.*

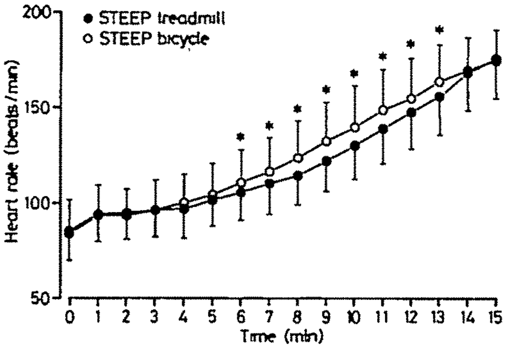

*Figure 2 Mean (SD) heart rate of 30 healthy men performing the two STEEP protocols. *$p < 0.05$ on uncorrected t test.*

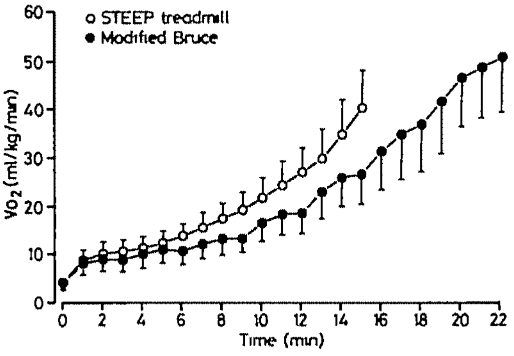

Figure 3 Mean (SD) oxygen consumption of 30 healthy men performing the two treadmill protocols. $\dot{V}O_2$, oxygen consumption.

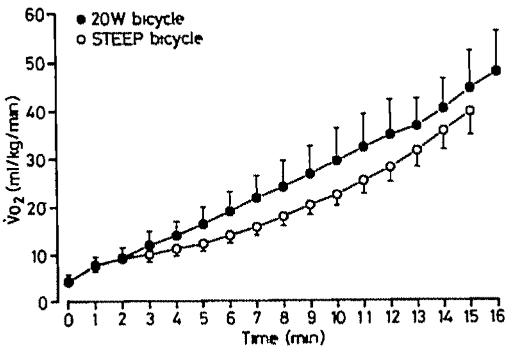

Figure 4 Mean (SD) oxygen consumption for 30 healthy men performing the two bicycle protocols. $\dot{V}O_2$, oxygen consumption.

modified Bruce protocol but not during subsequent stages. The mean (SD) exercise time on this protocol was 20 minutes 14 seconds (156 seconds), and the mean (SD) $\dot{V}O_2$ max was 45·3 (13·1) ml/kg/min.

Figure 4 compares the two bicycle protocols. The mean exercise time on the 20 W/min protocol was 12 minutes 29 seconds and the mean (SD) $\dot{V}O_2$ max was 38·2 (10·5) ml/kg/min. The between subject variability of oxygen consumption at each stage, as reflected by the standard deviation, was less with the STEEP bicycle protocol than with the 20 W/min protocol (fig 4).

Discussion

We have designed a new exercise protocol that is the first to be based on exponential rather than linear increments in workload. The test begins with a low workload and because it uses small, frequent increments it is suitable for even the most severely limited patients. Nevertheless, it is designed to induce cessation of exercise in patients with $\dot{V}O_2$ max up to 35 ml/kg/min within 15 minutes so that boredom and fatigue are not limiting factors. To allow measurement of oxygen consumption over the full 15 minute protocols the STEEP tests were initially validated in healthy men rather than the patient population for which they are designed. Both STEEP tests produced a gradual exponential rise in oxygen consumption in these healthy subjects, and no plateau in the cardiovascular responses was apparent.

For 11 of the 15 stages of the treadmill and bicycle tests the mean $\dot{V}O_2$ was the same. Oxygen consumption was slightly higher during the first 3 minutes of the treadmill protocol, possibly because the initial treadmill speed was considerably slower than the subjects' normal walking pace, causing them to adopt an inefficient gait. $\dot{V}O_2$ was also higher on the treadmill during the final stage of exercise. This may be because some subjects performing the bicycle test had already reached their $\dot{V}O_2$ max and were therefore unable to increase their oxygen consumption further during the last stage of the protocol.

Our finding that the $\dot{V}O_2$ max with the 20 W/min bicycle protocol was lower than with the modified Bruce test accords with previous studies that showed $\dot{V}O_2$ max was 6%–17% lower on a bicycle ergometer than on a treadmill.[2 7–9] Possible reasons for a lower $\dot{V}O_2$ max on a bicycle ergometer include an early end to exercise because of localised fatigue and pain in the quadriceps.[10] In addition, the maximum cardiac output was lower during bicycle exercise,[7] and this resulted in a lower $\dot{V}O_2$ max because oxygen consumption is proportional to cardiac output.[11 12] During submaximal stages the heart rate during the STEEP bicycle protocol was higher than during the treadmill protocol, despite similar oxygen consumption. This suggested a lower stroke volume during bicycle exercise as was reported in previous studies.[10 13 14]

Many existing protocols have relatively long stages of two or three minutes each in an attempt to produce a plateau of oxygen consumption at each stage. The time taken to reach a steady state is variable, however, and depends on the physical fitness of the subject and the relative work intensity.[13 15] The effect of this was illustrated in this study: during the modified Bruce protocol a steady state was reached rapidly during the early stages but not at all during later stages. Thus a true steady state may not be achieved during the the final stage of an exercise test. Another problem with tests consisting of a few prolonged stages is that patients become familiar with the protocol during repeat testing and may repeatedly stop exercising at the same stage. This learning effect may mask improvement with treatment.[3] We therefore designed a protocol with small, frequent increases in workload, as recommended by previous researchers.[2,16] This type of protocol is very useful if submaximal exercise testing is planned later. When a protocol with small, frequent increases in workload has been used for a maximal test, it is possible to choose a stage at 60%–70% of that subject's $\dot{V}O_2$ max for a subsequent submaximal test. A further advantage of the STEEP treadmill test over existing treadmill protocols is that it avoids simultaneous increases in speed and gradient which can unsettle patients.[17]

The mean exercise time of 12 minutes 29 seconds for the 20 W/min bicycle protocol was appropriate for these normal subjects; the test would be too short for severely limited patients, however. Furthermore, because body weight is not taken into account, the oxygen consumption at each stage varied considerably between subjects. With the 20 W/min bicycle protocol it is therefore not possible to determine whether a patient's exercise time is impaired or to measure the degree of impairment without correction for body weight or direct measurement of oxygen consumption during the test. The STEEP bicycle test takes account of body weight and therefore produces less interpatient variability.

We designed a new protocol based on short stages with exponential increments in workload. The potential advantage of this protocol is that it is suitable for a wide range of patients. The most severely limited patients should manage the initial low workloads, while the exponential rise in workload terminates the test within 15 minutes before boredom and fatigue become limiting factors. The treadmill test is unlikely to intimidate patients because the increments are small and simultaneous increases in speed and gradient are avoided. The test can also be used on a bicycle ergometer if an allowance is made for body weight. In healthy subjects we obtained close agreement between the mean oxygen consumptions for each stage with both modes of exercise. It remains to be seen whether this will be true in a representative patient population.

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Plasma concentration of atrial natriuretic peptide in spontaneous atrioventricular re-entrant tachycardias of childhood

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Abstract

Plasma atrial natriuretic peptide was measured in 13 children between the ages of 1 week and 2 years 9 months during atrioventricular re-entrant tachycardia and 15 minutes after the restoration of sinus rhythm. There was a significant decline in atrial natriuretic peptide during sinus rhythm. Plasma concentrations of the peptide were significantly higher during tachycardia in seven infants under 1 year than in the six older children. The heart rates and the duration of tachycardia were not significantly different in the two age groups. Cardiac failure was present in five of seven children under 18 weeks of age during tachycardia but in none of the older children. The plasma concentration of atrial natriuretic peptide did not significantly correlate with duration of tachycardia or heart rate. If tachycardia occurs in young infants the low functional reserve capacity of the developing heart leads to cardiac failure more frequently and it is likely that this was the cause of the significantly higher plasma concentration of atrial natriuretic peptide in the younger children.

Atrial natriuretic peptide, a 28 amino acid peptide, is released from the atria in response to distension.[1 2] Plasma concentrations of atrial natriuretic peptide were increased during supraventricular[3-5] and ventricular[3 6] tachycardia in adults, probably because of increased atrial tension.[7 8] The increased plasma concentration during tachycardia caused diuresis and natriuresis by increasing the glomerular filtration rate and decreasing aldosterone secretion.[8] We are not aware of any studies on plasma atrial natriuretic peptide during tachycardias in children. The physiological response of the developing heart to tachycardia differs from that of adults[9 10] and cardiac failure is a more common accompaniment.[11] We tested the hypothesis that atrial natriuretic peptide release in response to tachycardia in infants also differed from that in older children by measuring plasma concentration during tachycardia and 15 minutes after restoration of sinus rhythm in 13 patients (age range 1 week to 2 years 9 months). We hoped to define further which factors were the most important in causing release of the peptide during tachycardia.

Data on patients

Case	*Age*	*Heart rate in tachycardia (beats/min)*	*Duration of tachycardia*	*Dose of adenosine (mg/kg)*
1	1 wk	280	6 h	0 1
2	2 wk	300	24 h	0 2
3	2 wk	300	8 h	0 25
4	7 wk	250	5 days	0 3
5	8 wk	290	24 h	0 2
6	16 wk	300	2 days	0 3
7	17 wk	240	1 h	0 3
8	12 mnth	240	2 h	0 3
9	13 mnth	260	10 min	0 1
10	20 mnth	280	6 h	0 15
11	24 mnth	300	12 h	0 15
12	28 mnth	270	3 h	0 1
13	33 mnth	270	4 h	0 1

Patients and methods

PATIENTS

The table shows data on the patients. Patients 2 to 6 were in heart failure when blood samples were taken. Patient 9 had undergone Mustard's repair for transposition of the great arteries. Patient 12 had Fallot's tetralogy but had not undergone surgery. The other patients all had normal intracardiac anatomy. All patients presented with atrioventricular re-entrant tachycardias.

METHODS

In young infants the onset of tachycardia was taken as the time when the child was first noted to be unwell with breathlessness and poor feeding. In older children it was taken from the time of complaint of feeling unwell. In the postoperative patient the tachycardia was noted while the patient was being monitored in the intensive care unit. In all patients echocardiography was performed to assess intracardiac anatomy. The presence of hepatomegaly or a raised jugular venous pressure was taken to indicate cardiac failure. Each patient was examined by two clinicians. Blood pressure and respiratory rate were measured during tachycardia and after restoration of sinus rhythm. The heart rate was calculated from the RR interval on the electrocardiogram.

The blood samples (1 ml) were taken during tachycardia when the peripheral venous line was placed. A further blood sample (1 ml) was taken from the line (after removal of an adequate dead space) 15 minutes after the restoration of sinus rhythm. In view of the age of the patients, sampling was restricted to these occasions. The samples were collected into tubes containing ethylenediaminetetraacetic acid at 1 mg/ml and aprotinin at 1000 kallikrein inactivator units/ml. They were placed on ice and immediately centrifuged. The plasma was withdrawn and frozen at −70°C.

Atrial natriuretic peptide was extracted from 0·5 ml of plasma using a C_8 reverse phase cartridge (Amersham, UK) according to the method developed by Amersham. Mean (SD) recovery of ^{125}I-peptide added to plasma was 87 (3)% (n = 10). Atrial natriuretic peptide concentrations were by radioimmunoassay with a combination of rabbit antiserum generated against human 1-28 atrial natriuretic peptide (Peninsula Laboratories, St Helens) and ^{125}I-labelled human atrial natriuretic peptide (2000 Ci/mmol, Amersham, UK) as the tracer.[12] To cope with the small sample volumes available from paediatric patients, plasma extracts were reconstituted in 0·25 ml of assay buffer and assayed in triplicate by a low volume disequilibrated assay: 50 μl of antibody was incubated with 50 μl of standard (0·5–50 pg/tube) or extract for 24 hours at 4°C. Tracer peptide was then added (approximately 6000 cpm) and the mixture incubated for a further 24 hours at 4°C. Free and bound tracer were separated by the addition of 100 μl of a 1:20 dilution of donkey antirabbit antiserum containing 0·5% normal rabbit serum (Guildhay Ltd, Guildford) followed by an overnight incubation at 4°C. After centrifugation for 45 minutes at 4°C and 3000 *g*, the precipitate was counted on a twin-head gamma counter (LKB, Finland). Assay buffer comprised 0·05 mol/l tris-HCl pH 7·6, containing 0·3% (W/V) bovine serum albumin (RIA grade, Sigma, UK) and 0·1% Triton X-100 (Sigma, UK). Standard curves were constructed in assay buffer from a stock of the international standard for human atrial natriuretic peptide (code 85/669, NIBSC, London). The antiserum was used at 1:5 of the dilution recommended by Peninsula. This produced an overall assay sensitivity of 1 pg/tube (determined as the peptide concentration giving a 10% decrease in binding) and intra and inter assay variations of 10% (n = 10) and 19% (n = 21) respectively. Related samples from the same patient were always included in the same extraction run and assay.

We used non-parametric tests for statistical analysis. A Wilcoxon paired analysis was performed to determine whether there was a significant decline in atrial natriuretic peptide after restoration of sinus rhythm. A Mann-Whitney test was used to compare plasma concentrations during tachycardia in young infants with those in older children and to compare the heart rates and duration of tachycardia in these two groups. Spearman's rank correlation coefficient was used to assess the relation between plasma atrial natriuretic peptide during tachycardia and the age of the patient, duration of tachycardia, and heart rate. The correlation between the plasma concentration and the dose of adenosine given to patients was calculated similarly. Ethical approval was obtained from our hospital ethics committee.

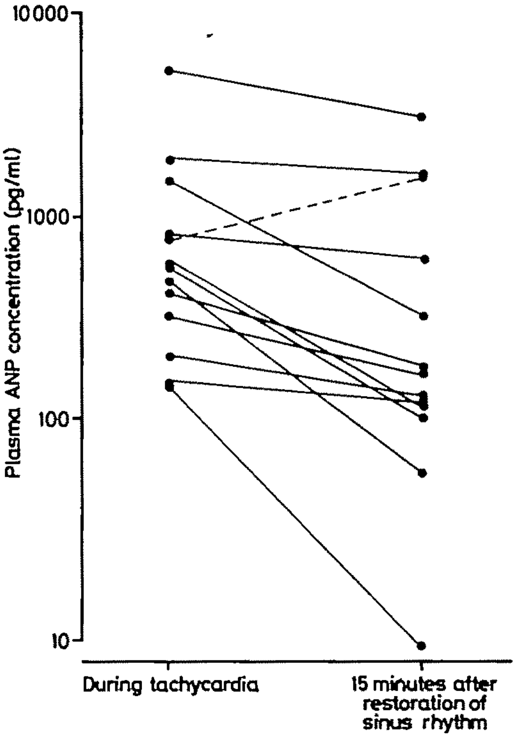

Figure 1 Changes in plasma atrial natriuretic peptide (ANP) 15 minutes after restoration of sinus rhythm in 13 children with spontaneous tachycardia.

Results

Adenosine was given in incrementally increasing doses of 0·05 mg/kg from 0·05 mg/kg to 0 3 mg/kg to all patients. Patients 4, 6, and 7 did not respond to adenosine despite maximal dosages of 0·3 mg/kg. In these patients tachycardia was terminated with flecainide. After intravenous flecainide and despite restoration of sinus rhythm patient 5 became hypertensive, poorly perfused, and the cardiac failure worsened (as assessed by hepatomegaly).

Figure 1 shows the plasma concentrations of atrial natriuretic peptide for each patient both during tachycardia and after restoration of sinus rhythm. The decline in plasma concentration after the end of tachycardia was significant ($p < 0·02$). There was no significant correlation between plasma atrial natriuretic peptide during tachycardia and the duration of tachycardia. There was a weak positive correlation between heart rate and plasma concentration (0·29) and a weak negative correlation between age and plasma concentration (−0·38); neither correlation was significant. When considered as a group, however, the children under 1 year of age had significantly higher plasma concentrations of atrial natriuretic peptide than the older children ($p < 0·02$, 96·2% confidence interval from 154 to 1839 pg/ml). Figure 2 shows the plasma concentrations of atrial natriuretic peptide during tachycardia plotted against age. There was no significant difference between either the heart rates or the duration of tachycardia of the two age groups. Blood pressure and respiratory rate did not change significantly after restoration of sinus rhythm.

There was a positive correlation between the

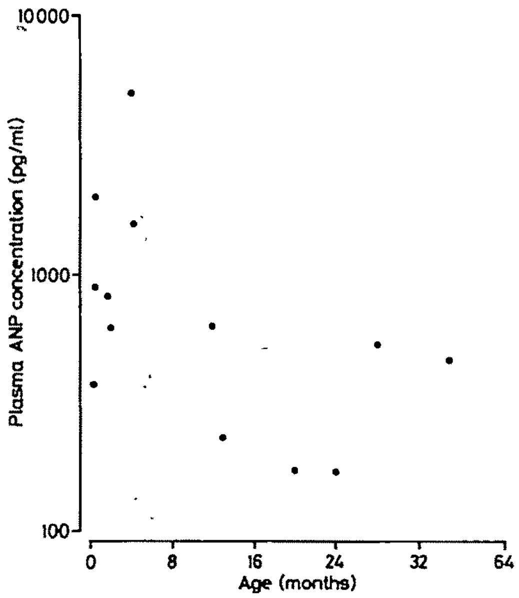

Figure 2 Distribution of plasma atrial natriuretic peptide (ANP) during tachycardia with age in 13 children.

dose of adenosine used to terminate atrioventricular re-entrant tachycardia and plasma atrial natriuretic peptide during the tachycardia (r = 0·57). The correlation coefficient was increased (r = 0·58) and was significant at the 5% level when the three patients (4, 6, and 7) who were unresponsive to the maximum dose (0·3 mg/kg) of adenosine were included.

Discussion

The findings in our study accorded with the results in adults in whom there was a significant and rapid decline of plasma atrial natriuretic peptide after restoration of sinus rhythm.[4] In addition, we showed that the absolute plasma concentrations during tachycardia were significantly greater in infants than in older children. Why is there a difference between the two groups? One factor may be the duration of tachycardia. Early detection of an arrhythmia is difficult in the very young patient and the longer duration of tachycardia may lead to continued release of atrial natriuretic peptide. We do not believe this to be the case because our younger patients did not have a significantly longer period of tachycardia than the older children. This seems to support animal work that showed a decline in plasma concentrations of the peptide during sustained rapid cardiac pacing.[13]

Others suggested that the high tachycardia rate may be a factor in the increased release of the peptide.[14] While it is true that the atrioventricular node is capable of faster conduction in infancy,[15] we found no significant difference between tachycardia rates in infancy and early childhood.

A possible explanation for the significantly higher concentrations in our younger patients is that they have greater stores of atrial natriuretic peptide. Plasma concentrations are high in healthy newborn infants and they decrease during the first week of life.[16] We found no significant correlation between plasma concentration and age per se, however; and only when the infants were considered as a group did they have significantly higher concentrations than the older children.

The young infant often presents in cardiac failure as a result of tachycardia.[11] Five of the seven infants in our study were in heart failure at presentation, but none of the older children was. The plasma concentration of atrial natriuretic peptide increased in adult patients with congestive cardiac failure and the plasma concentration seemed to be directly related to right atrial pressure.[17 18] The effect of heart failure on plasma concentrations of atrial natriuretic peptide was further illustrated by our findings in one infant in whom cardiovascular collapse and worsening cardiac failure occurred after intravenous flecainide, probably because of the negative inotropic effect of the drug.[19] In this patient, plasma atrial natriuretic peptide increased despite restoration of sinus rhythm. We believe that the increased incidence of heart failure in the infants we studied was the likely cause of their raised plasma concentrations of atrial natriuretic peptide.

At our hospital, adenosine is used to treat re-entrant tachycardia in children.[20] We found the dose given correlated significantly with the plasma concentration of the peptide. This may merely represent the finding that the children with the highest concentrations of the peptide are those with the more severe cardiac failure and therefore with the greatest sympathetic drive to their atrioventricular node. Alternatively, there may be a direct interaction between adenosine and atrial natriuretic peptide. Further studies are needed to clarify this.

The changes we have shown in plasma atrial natriuretic peptide define the pattern of release in childhood tachycardias and reflect the differing response of the infant heart to disturbances of rhythm. Atrial natriuretic peptide is beginning to be used as a therapeutic agent in adults.[21 22] Before it is used in children, a clearer understanding of the pathophysiology is essential.

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Operative findings after percutaneous pulmonary balloon dilatation of the right ventricular outflow tract in tetralogy of Fallot

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Abstract

Since 1983 percutaneous balloon dilatation of the right ventricular outflow tract has been performed as an alternative to surgical palliation in selected cases of tetralogy of Fallot at the Royal Liverpool Children's Hospital. From 31 December 1984 to 31 December 1988, 27 of these patients underwent subsequent surgical correction. Age at operation ranged from 7 to 58 months (median 2·7 years). The mean interval between balloon dilatation and correction was 15·6 months (range 3–39 months). Two patients had a systemic pulmonary shunt operation performed before dilatation and a further five required one afterwards. Overall 20 (74%) patients had some anatomical alteration as the result of balloon dilatation, while in seven (26%) there was no discernible change in the right ventricular outflow tract. There was no consistent relation between the ratio of balloon size to pulmonary annulus diameter and the morphological findings.

Balloon dilatation may obviate the need for systemic-pulmonary shunt at the expense of some structural damage, particularly to the posterior cusp. The present data suggest that dilatation does not bring about growth of the annulus to such an extent that transannular patch is no longer needed at intracardiac repair.

Since percutaneous pulmonary balloon dilatation was introduced in 1953,[1] it has become the treatment of choice for pulmonary valve stenosis in many centres. As suggested initially by Semb *et al*[2] and Kan *et al*,[3] the haemodynamic results compare favourably with those of surgery, especially when dysplastic valves are excluded. Because of this, few patients come to operation and the numerous published series[4–6] contain little information on the morphological effects of dilatation of the right ventricular outflow tract.[5 7 8]

In our hospital, percutaneous pulmonary balloon dilatation has been practised as an alternative to or in combination with surgical palliation in selected patients with tetralogy of Fallot.[9] Because most of these patients will eventually undergo operation we were presented with an opportunity to observe the anatomical consequences of dilatation of the right ventricular outflow.

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Patients and methods

From 31 December 1984 to 31 December 1988, 27 patients underwent correction of tetralogy of Fallot after previous balloon dilatation of the right ventricular outflow tract. This includes 15 of those reported in the original clinical series.[9] We reviewed the clinical notes; the operative reports; and, when available, the necropsy specimens.

The median age of the patients at operation was 33 months (range 7–58 months). Twenty one of them had one pulmonary dilatation, four had two procedures, and two patients had three and four balloon dilatations. The mean age at the first dilatation was 10·0 months (range 0·5–30); for all dilatations the median age was 14·6 months (range 0·5–56). Balloon sizes ranged from 5 to 15 mm (mean 13 mm). Surgical correction was undertaken 3 to 39 months (mean 15·6 months) after dilatation.

At operation the surgeon classified the pulmonary valve leaflets as follows: (*a*) *intact,* when there was no observable effect of dilatation; (*b*) *detached,* when the leaflet was separated from its hinge-point for a variable length, starting from one of the commissures; (*c*) *split,* when a vertical tear was found, usually in mid-portion of the leaflet dividing it in two segments (in no case was a split identified at a commissure); (*d*) *fused,* when the leaflets were fused to the pulmonary artery wall, probably after initial detachment.

The pulmonary ventriculo-arterial junction (pulmonary annulus) was described as: (*a*) *intact,* where there was no observable effect of dilatation; or (*b*) *split,* when there was a tear usually originating at the hinge-point of the leaflet and extending a variable distance into the main pulmonary artery and its right branch.

The computerised records of all the other patients (113) who underwent correction of tetralogy of Fallot over the same period (31 December 1984–31 December 1988) and who did not have balloon dilatation were reviewed to determine how many later had systemic-pulmonary shunt operations performed at our hospital or elsewhere and how many required a transannular patch at the time of correction.

All patients underwent intracardiac repair of tetralogy of Fallot by standard surgical techniques on conventional cardiopulmonary bypass. In most patients we used accepted criteria for the predicted ratio of postoperative right and left ventricular pressures to decide whether or not a transannular patch was required. The ventricular septal defect usually was closed through the right atrial approach.

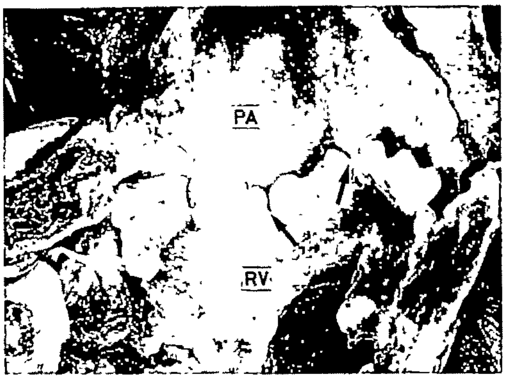


Figure 1 Posterior leaflet of pulmonary valve after percutaneous pulmonary balloon dilatation showing the frequently encountered vertical tears (split leaflet) (arrows). More often, however, this consisted of a single tear from free edge to the hinge-point of the cusp. RV, right ventricle; PA, pulmonary artery.

Table 1 Findings at operation

Morphology	*n*	%	*70% CI (%)*
Leaflets:			
Intact	7	26	17–37
Detached	8	30	20–41
Split	9	33	23–45
Fused	8	30	20–31
Annulus:			
Intact	22	81	71–89
Split	5	19	11–29

Table 2 Relation between ratio of balloon size to pulmonary artery annulus and operative findings in terms of patient numbers and the results of logistic regression analysis of the stratified results

	Operative findings		
Balloon/PA range (%)	*Morphological damage (n)*	*Intact (n)*	*Total*
<120	4	3	7
121–140	2	2	4
141–160	6	1	7
161–180	1	1	2
181–200	4	0	4
>201	1	0	1
Totals	18	7	25*

Constant (SE)	Balloon/PA ratio (SE)	t	df	p
−0·49 (0·87)	0·58 (0·38)	1·52	23	<0·2

*Two patients had catheterisation without recorded angiography
PA, diameter of pulmonary artery annulus.

We used simple logistic regression analysis to examine whether the ratio of balloon size to pulmonary artery diameter predicted morphological changes in the pulmonary artery. We analysed the frequency of transannular patch and shunt operations in patients treated by dilatation and those who were not by the χ^2 test. We regarded p values of between 0·05–0·1 as statistically significant. We calculated the 70% confidence intervals for all percentages.

Results

Table 1 shows the findings at operation. Figure 1 is an example of a split leaflet. Overall 20 of the patients (74%) (70% CI 63%–83%) had gross evidence of damage caused by balloon dilatation. Seven patients (26%) (70% CI 17%–37%) had an intact outflow. Only five (19%) (70% CI 11%–29%) had evidence of changes that extended to more than one morphological category. No valve was found to have been split along a commissure and most valves described as "intact" were still obstructive with fused commissures. In five (19%) (70% CI 11%–29%) there was a posterior split of the pulmonary arterial wall (fig 2), starting at the ventriculo-arterial junction and often extending into the right branch. In one of the patients who died, gross and microscopical examination showed extensive disruption of the tissues (fig 3). The endothelial continuity was lost posteriorly at the depressed and uneven area that corresponded with the macroscopic tear, although the adventitia remained intact. Subendocardial fibrosis and elastosis were conspicuous in all sections of the adjacent right ventricular outflow septum in this patient.

Table 2 shows the relation between the ratio of the balloon size to the angiographic diameter of the pulmonary annulus and the frequency of

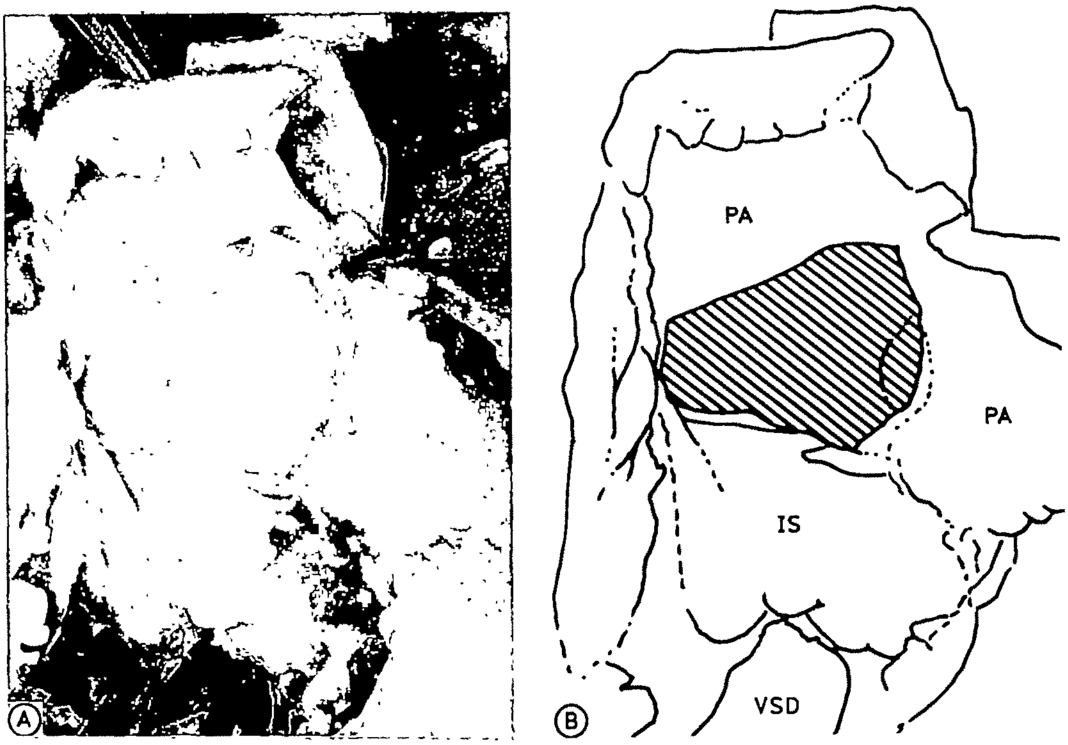


Figure 2 Posterior aspect of main pulmonary trunk opened anteriorly. The pulmonary valve leaflets were excised intraoperatively. The ventricular septal defect patch has been removed. The tear in the arterial wall (shaded area of corresponding diagram) shows the loss of endothelial continuity PA, pulmonary artery; IS, infundibular septum; VSD, ventricular septal defect.

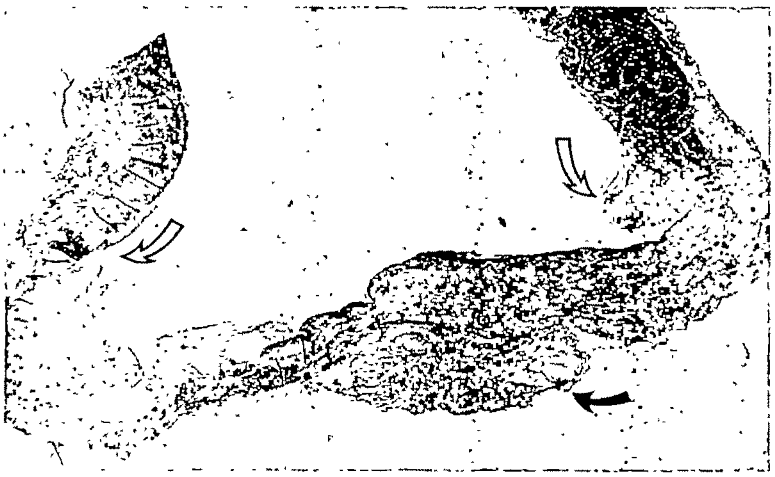
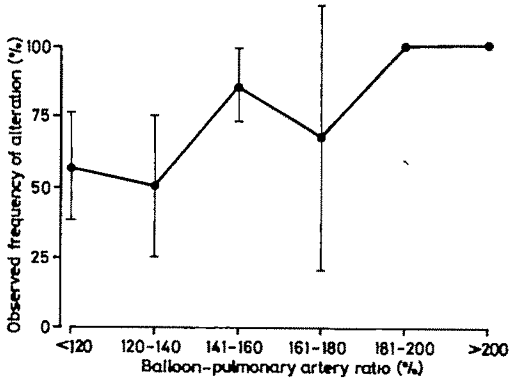


Figure 3 Photomicrograph of a transverse section through the shaded area of the specimen shown in fig 2. There was a loss of endothelial wall continuity in the central depressed area (between open arrows). There were masses of eosinophilic degenerated tissue in the underlying fibroelastic corion. The adventitia was intact (closed arrow). Haematoxylin and eosin stain, original magnification × 3.

Figure 4 Observed frequency of alterations in the pulmonary valve/ventriculo-arterial junction, according to the ratio of balloon size to angiographic pulmonary annulus diameter. The bars show the 70% confidence interval of each proportion.



morphological change. Simple logistic regression analysis showed no relation between these two variables. None the less, there tended to be less damage with smaller balloon ratios (fig 4). The largest group with intact valves (n = 3) had balloon/annulus ratios of <120%.

Eighteen patients (67%) (70% CI, 56%–77%) required a transannular patch at the time of correction; and two (one after a limited transannular patch because of coronary artery anomalies) had an extracardiac conduit. There were three operative deaths. Two patients with classic tetralogy of Fallot died of low cardiac output, one of them with myocardial infarction resulting from a coronary artery injury. The third patient who died had Down's syndrome, tetralogy of Fallot, and a complete atrioventricular septal defect. He developed raised pulmonary vascular resistance and congestive heart failure after balloon dilatation of a stenosed Blalock shunt and the right ventricular outflow. The right ventricle proved inadequate to sustain the circulation postoperatively. Figures 2 and 3 show the heart from this patient.

Forty one (36%) of the 113 patients in the "control" group who did not have balloon dilatation (70% CI 31%–42%) had had a systemic pulmonary anastomosis before correction. A total of 26 (63%) patients had one palliative operation, 14 (34%) had two, and one (2%) had three operations. Shunt operations were thus significantly more common in the non-dilatation group (χ^2 = 3·12, p = 0·08), and fewer patients had surgical palliation when balloon dilatation had been performed. A transannular patch was required in 62 (55%) of the group without prior balloon dilatation (70% CI, 50%–60%) and in 18 (67%) of 27 of the dilatation group (70% CI, 55%–77%) (χ^2 = 27, p = 0·27).

Discussion

Balloon dilatation of the pulmonary valve is an invasive, non-surgical technique[1-3] used to relieve obstruction of the right ventricular outflow tract.[4-6] The ideal balloon size, the number and pressure of inflations, and patient selection vary among different centres. Except for the report on the effect of balloon dilatation of the pulmonary annulus on newborn lambs from Ring and colleagues[10] and mention of isolated surgical cases in series of pulmonary valve dilatations,[7 8] there is little information available on the morphological consequences of the procedure on the right side of the heart. This, in part, attests to its relative safety and effectiveness, because few patients who have undergone dilatation of isolated pulmonary valve stenosis required later surgery.

Ring showed that balloon inflation severely damaged the right ventricular outflow tract in newborn lambs particularly when the balloon diameter was >50% bigger than the pulmonary artery diameter.[10] In animals killed 83 and 111 days after dilatation the damaged area was occupied by small patches of fibrosis. We did not find distinctive signs of this type of trauma in our patients at operation but in most patients with tetralogy of Fallot the endocardium in areas of turbulence is usually whitened and fibrotic. We have not examined enough patients to know whether fibrosis along the right ventricular outflow (which cannot be solely attributed to the dilatation scar) will predispose to ventricular arrhythmias—as was suggested by Ring[10] commenting on the clinicopathological study by Deanfield and colleagues.[11] By using simple logistic regression analysis, we were unable to show any significant relation between the size of the balloon and occurrence of morphological changes (table 2), except for the general trend shown in fig 3. However, in one four month old patient, who has not yet come for correction (and therefore is not included in this report) sudden and severe hypotension and hypoxia after balloon dilatation required urgent systemic-pulmonary artery anastomosis. After the chest was opened, blood was evacuated from a tense pericardium and we found disruption of the anterior right ventricular outflow tract with a large subadventitial haematoma extending across the annulus into the left pulmonary artery. Follow up catheterisation showed a small, round diverticulum protruding from the anterior aspect of the right ventricular outflow tract, confirming an extensive structural deformity.

The major changes in our series were confined to the valve leaflets; 20 (74%) of patients (70% CI, 63%–83%) had one or more of the changes described, while 22 (81%) (70% CI, 71%–89%) were free of annular/pulmonary artery disruption. The frequency of the three categories of cusp alterations was very similar (table 1). It is striking that most of the morphological changes were found on the posterior leaflet and the posterior wall of the pulmonary trunk. We have not found an obvious explanation for this; but suggest that because this area has direct attachments to supporting structures, it would be less likely to distend under the balloon pressure and therefore would be more likely to tear or split. The anterior aspect probably is more elastic and compliant and would therefore stretch under pressure. Lock *et al* found multiple intimal tears in the lesions of lambs killed <3 days after dilatation of experimentally created branch pulmonary artery strictures.[12] In some cases, these extended through all the arterial layers except the adventitia. In lambs killed 7 days after the procedure, all the tears were healed and the intima and media were intact; but the area of the old medial haemorrhage continued to show separation of fibres, with the blood replaced by smooth muscle cells. In view of the interval between dilatation and operation in our patients, we expected to find an avascular, fibrous area posteriorly at the site of previous intimal disruption. The long term importance, if any, of this alteration in the pulmonary outflow is uncertain.

The pattern of use of transannular patches was similar in patients who had operations for tetralogy of Fallot at our hospital during the same period as the group who had had balloon dilatation. Judged on the need for a transannular patch, we did not find that balloon dilatation resulted in appreciable growth of the pulmonary annulus. But because our study group contained few patients with angiograms both before and after dilatation we cannot be certain. It was also our impression that it was more difficult to achieve a competent pulmonary valve mechanism after balloon dilatation. Though the posterior cusp may be used to appose an anterior monocusp patch or some valve function can be achieved through a "two cusp plasty" technique,[13] this was often thwarted by disruption of the posterior cusp. When we analysed the incidence of a systemic to pulmonary shunt in both groups, we included only patients in whom shunting was necessary after attempted palliation by balloon dilatation. Over a third (36%) (70% CI, 31%–42%) of the control patients had one or more shunt operations performed before correction compared with 19% (70% CI, 11%–29%) in the study group which could be interpreted as showing that in 81% of patients (70% CI, 71%–89%, $n = 22$) a shunt was avoided, because satisfactory palliation was achieved by balloon dilatation. But the two groups were not strictly comparable in their underlying morphology, symptoms, or indications for palliation. A more rigorous, prospective randomised trial is necessary to compare accurately the role of percutaneous pulmonary balloon dilatation with surgical palliation for Fallot's tetralogy.

Given the present surgical thrust towards conservation of right ventricular and pulmonary valvar function, by means of a transatrial repair in tetralogy of Fallot,[14] it is possible that palliation also should be directed towards conservation of the pulmonary valve mechanism. The long term effects of cusp damage in patients who did not require a transannular patch remain to be determined. However, accumulating evidence suggests that continuing pulmonary regurgitation may be detrimental to right ventricular function.

We found that balloon dilatation tended to split the posterior pulmonary valve leaflet or detach it from the hinge point, with or without a dehiscence in the posterior wall of the pulmonary artery. This may obviate the need for a systemic-pulmonary shunt, possibly at the expense of some anatomical damage and loss of valvar function at later correction. In view of these findings, we advise that the balloon size should be limited to 120%–140% of the diameter of the pulmonary annulus. From our present data, we cannot tell whether dilatation has any effect on the growth of the pulmonary arteries,[15] but the procedure did not seem to alter the need for a transannular patch at the time of intracardiac repair.

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Tetralogy of Fallot with anomalous pulmonary venous connections: a rare but clinically important association

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Abstract

Anomalous pulmonary venous connections were found in seven (0·6%) of 1183 patients with tetralogy of Fallot. Three patients had totally anomalous connections (one supracardiac, one direct to coronary sinus, and one mixed supracardiac and infracardiac) and four patients had partially anomalous pulmonary venous connections. All patients presented with the clinical features of tetralogy of Fallot. Anomalous pulmonary venous drainage was suspected clinically in only one patient in whom there was a scimitar sign on the chest radiograph. The exact diagnosis was established by cross sectional echocardiography (one), preoperative or postoperative angiography (five), or at necropsy (one). Surgery was performed in six patients. Total correction without re-routing of the anomalously draining veins was successful in all those with partially anomalous connections, with no significant long term sequelae (follow up median 17 years). Of those with totally anomalous connections, the full diagnosis was made only at necropsy in one patient, successful one-stage correction was performed in one, and the other patient, who had partially obstructed mixed drainage, died shortly after one-stage correction. Histological examination of the lung biopsy specimen in this patient showed grade 2 pulmonary vascular disease.

Tetralogy of Fallot with anomalous pulmonary venous connections is a rare association. Careful preoperative assessment is required in those with totally anomalous connections.

There are scattered reports describing the association of tetralogy of Fallot with totally anomalous pulmonary venous connections.[1-3] With fewer than 10 published cases this is an infrequent association that is rarely suspected clinically. Its diagnosis by cross sectional echocardiography has not been reported, but the complete diagnosis has been made at the time of cardiac catheterisation,[4] corrective surgery,[5] or necropsy.[6] Furthermore, there are few data on the incidence and association of tetralogy of Fallot with partially anomalous pulmonary venous connections.[1] We reviewed all cases of tetralogy of Fallot with anomalous pulmonary venous connections seen at the Brompton and National Heart Hospitals in the past 20 years.

Patients and methods

We reviewed the records of 1183 patients with a diagnosis of tetralogy of Fallot investigated at the Brompton and National Heart Hospitals in the past 20 years. Only patients with atrial situs solitus were reviewed; we excluded those with isomerism of the atrial appendages.

Seven patients (0·6%) had abnormalities of pulmonary venous connection. Their ages at presentation ranged from three days to four months. In only one was the complete diagnosis made by cross sectional echocardiography. In the remainder the diagnosis was made either at the time of cardiac catheterisation (four patients), corrective surgery and later cardiac catheterisation (one), or at necropsy (one).

Case reports

The table gives the clinical data, full sequential diagnosis, and outcome for each of the seven patients.

THREE CASES OF TETRALOGY OF FALLOT WITH TOTALLY ANOMALOUS PULMONARY VENOUS CONNECTION

Case 1

A 3 year old boy, cyanosed from early infancy, was referred after cardiac catheterisation elsewhere. The cineangiograms confirmed the presence of tetralogy of Fallot with severe obstruction of the right ventricular outflow tract caused by anterior deviation of the outlet septum and stenosis of the pulmonary valve. Selective injections into normal-sized right and left pulmonary arteries showed unsuspected mixed pulmonary venous connections, the right lower lobe and all the left sided pulmonary veins forming a confluence and draining infradiaphragmatically, and the right upper and middle pulmonary veins draining to the superior caval vein at its junction with the innominate vein (fig 1). Haemodynamic measurements showed that the pulmonary artery pressure was 45/22 mm Hg with right and left ventricular pressures of 75/8 mm Hg. His aortic oxygen saturation was 73%.

Complete correction of tetralogy of Fallot with anastomosis of the pulmonary venous confluence to the left atrium was performed. A stenosis of the insertion of the right upper and middle pulmonary veins into the superior

Data on each of the seven patients

Case	*Sex*	*Age at presentation*	*Clinical features*	*Associated abnormalities*	*Operation*	*Outcome*
1	M	4 months	Cyanosis and heart murmur	Mixed supracardiac and infracardiac TAPVC	One-stage correction age 4	Died after operation. Lung histology showed grade 2 pulmonary vascular disease
2	M	12 hours	Dysmorphic features, cyanosis, respiratory distress, heart murmur	Absent pulmonary valve syndrome and TAPVC to coronary sinus	Not performed	Died of respiratory failure at 30 hours of age
3	M	3 days	Cyanosis and heart murmur	Supracardiac TAPVC, left vertical vein to innominate vein	One-stage correction age 9 months	Well 9 months after operation
4	M	4 months	Cyanosis and heart murmur	Scimitar syndrome. Right hemianomalous drainage to hepatic vein	Correction of TOF age 9 years	Well 1 year after operation
5	M	1 month	Cyanosis and heart murmur	Right upper lobe vein to SVC	Blalock-Taussig shunt age 3 months, correction of TOF age 18 years	Well 17 years after operation
6	F	4 months	Cyanosis and heart murmur	Right upper lobe vein to SVC	Waterston shunt age 7 years, correction of TOF age 9 years	Well 17 years after operation
7	F	2 months	Cyanosis, heart murmur, and respiratory tract infections	Right upper and middle lobe veins to SVC	Correction of TOF age 10 years	Short of breath on exertion 26 years after operation

TOF, tetralogy of Fallot, APVC, anomalous pulmonary venous connections, TAPVC, total anomalous pulmonary venous connections; SVC, superior vena cava.

caval vein was relieved by a patch but these veins were left to drain anomalously. The immediate postoperative course was complicated by severe recurrent and refractory pulmonary hypertensive crises. He died four hours after operation.

Necropsy confirmed a satisfactory surgical repair but histological examination of the lung parenchyma showed Heath-Edwards grade II pulmonary vascular disease with a considerable increase in arteriolar wall smooth muscle. There was no intimal hyperplasia or vessel obliteration.

Case 2

A full term baby (birth weight 2 9 kg) was born with multiple dysmorphic features including low-set ears, flat nose, absent left thumb, and a rudimentary fifth ulnar digit. He was referred at 12 hours of age because of severe cyanosis. He had been intubated and ventilated because of increasing respiratory distress and severe cyanosis (po_2 = 3 1 kPa in 50% inspired oxygen) despite infusion of prostaglandin E_2. The chest radiograph showed a normal heart size, pulmonary oligaemia, and hyperinflation of the left lung with mediastinal shift towards the right. Cross sectional echocardiography showed abdominal situs solitus, with a concordant atrioventricular connection. There was tetralogy of Fallot with features typical of absent pulmonary valve syndrome. There was severe infundibular stenosis and very large confluent main, right, and left pulmonary arteries. The pulmonary venous drainage was not clearly displayed.

There was rapid deterioration in the child's condition with gross obstuctive emphysema of both lungs. It was thought that surgical correction was inappropriate in view of his poor condition, severe respiratory symptoms, and probable chromosomal disorder and he died at 30 hours of age. Necropsy confirmed the underlying diagnosis of tetralogy of Fallot with absent pulmonary valve syndrome and also showed totally anomalous pulmonary venous connection to the coronary sinus. The pulmonary veins were small. Subsequent chromosomal analysis showed a deletion on chromosome 15 with a mosaic loss of the Y chromosome.

Case 3

A 3 day old neonate was referred because of persistent cyanosis. The clinical findings were compatible with isolated tetralogy of Fallot.

Cross sectional echocardiography showed features typical of tetralogy of Fallot. There was, in addition, supracardiac totally

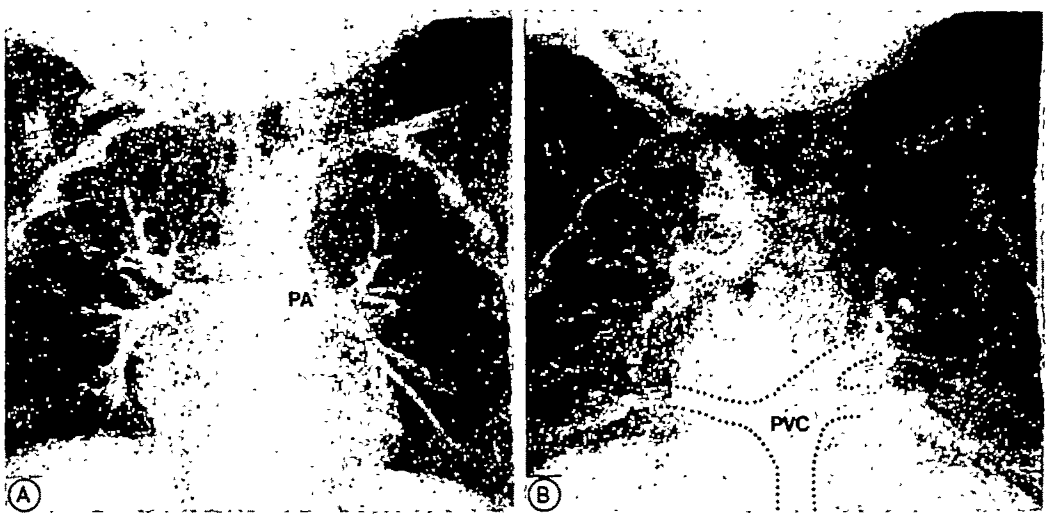

Figure 1 Selective pulmonary arteriogram (A) and laevophase examination (B) from patient 1. There was a mixed totally anomalous pulmonary venous connection. The pulmonary veins from the right upper and middle lobes drained directly to the superior vena cava. The right lower lobe vein drained to form a confluence with the veins from the left lung which drained infradiaphragmatically via a common vein. PA, pulmonary artery; PVC, pulmonary venous connection.

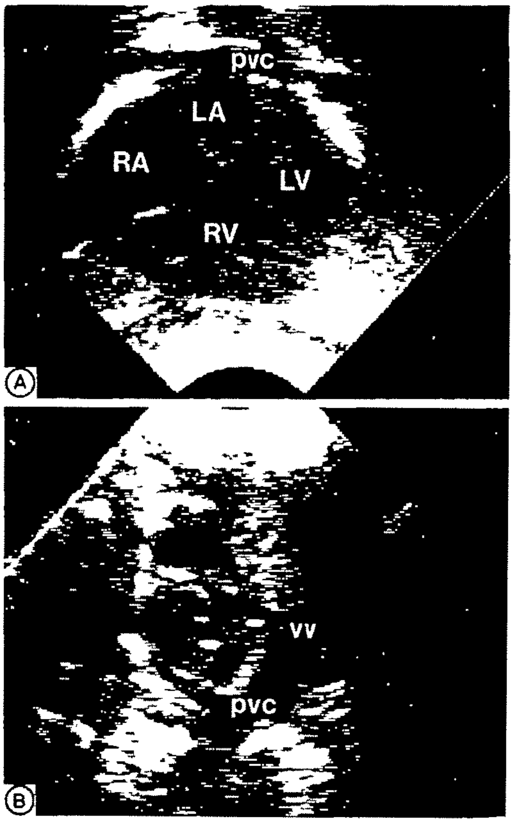

Figure 2 Cross sectional echocardiograms from patient 3. The subcostal 4 chamber section (A) shows the pulmonary venous confluence (pvc) outside the left atrium (LA). The suprasternal paracoronal section (B) shows the left vertical vein (VV) draining to the innominate vein. RA, right atrium; LV, left ventricle; RV, right ventricle.

anomalous pulmonary venous connection with the pulmonary venous confluence draining via a left sided vertical vein to the left innominate vein (fig 2). Phasic but low velocity flow was shown in the pulmonary veins by Doppler interrogation.

He remained moderately cyanosed but was otherwise well. Cardiac catheterisation was performed when he was nine months old to confirm that he was suitable for complete correction. Surgery was performed elsewhere when he was 10 months old. His early postoperative course was complicated by low cardiac output and bilateral pleural effusions which resolved during the first postoperative week. He has subsequently made a full recovery and is now symptom free nine months after operation.

TETRALOGY OF FALLOT WITH PARTIALLY ANOMALOUS PULMONARY VENOUS CONNECTIONS

All of the patients in this group presented with cyanosis in the first four months of life and had cardiac catheterisation before complete correction. Cross sectional echocardiography was performed before correction in only one patient (the others having been investigated before the introduction of the technique). In this case there was a hypoplastic right lung on the chest radiograph and no pulmonary veins that drained normally from the right lung could be shown by cross sectional echocardiography. Subsequent cardiac catheterisation with angiography showed a scimitar syndrome, with the pulmonary venous return from the hypoplastic right lung draining infradiaphragmatically to a hepatic vein. The right pulmonary artery was hypoplastic. The arterial blood supply to the right lower lobe was from an artery arising from the descending aorta (fig 3). The presence of anomalous venous drainage was noted in one other patient before operation (right upper lobe pulmonary vein to superior caval vein (patient 6). This patient made an uncomplicated recovery after a Waterston shunt performed at the age of seven years. In patient 7 anomalous drainage of right middle and upper lobe veins to the junction of the right superior caval and azygous veins was detected during a corrective operation. In patient 5 a right upper lobe vein draining to the right superior vena cava was shown only at routine postoperative cardiac catheterisation.

All of these patients have undergone successful complete correction of tetralogy of Fallot. There was no attempt to re-route the anomalous pulmonary veins in any of the patients. Follow up ranges from five months to 26 years (median 17 years). All are leading normal lives and three are entirely symptom free. One patient is short of breath on vigorous exertion (case 7). This patient was found to have an atrial septal defect of moderate size and residual obstruction of right ventricular outflow tract that required further operation. This was performed 23 years after the original repair; again no attempt was made to re-route the anomalous pulmonary veins.

Discussion

This study describes the clinical features and outcome of seven patients with tetralogy of Fallot and anomalous pulmonary venous connections. This was an uncommon association that occurred in 0·6% of the patients with tetralogy of Fallot seen at our hospitals in the past 20 years.

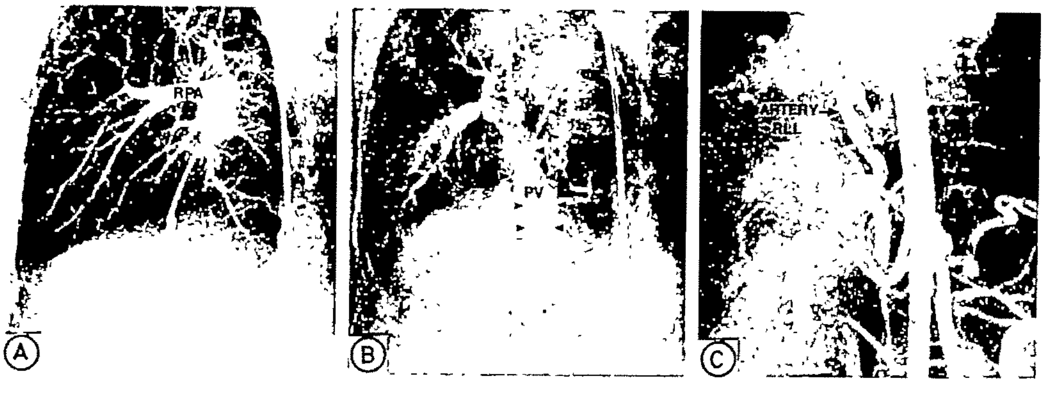

Figure 3 Selective right pulmonary arteriogram (RPA) from the patient with scimitar syndrome (A). Hemianomalous pulmonary venous drainage (PV) of the right lung infradiaphragmatically to the hepatic vein (B) An angiogram of the descending aorta (C). The systemic blood supply to the right lower lobe was abnormal (arrow).

All of the patients presented with clinical features compatible with isolated tetralogy of Fallot. This is because reduced pulmonary blood flow is the dominant lesion, even when pulmonary venous return is obstructed.[1] In only one patient, in whom there was a hypoplastic right lung and a scimitar vein on the chest radiograph, was the possibility of anomalous pulmonary venous drainage suspected clinically.

When there is totally anomalous pulmonary venous drainage early diagnosis of anomalous pulmonary venous return is particularly desirable, although previous reports have highlighted the difficulties in the non-invasive diagnosis of this association.[2,6] In one of our patients the diagnosis was established by cross sectional echocardiography, a pulmonary venous confluence and vertical vein draining to the innominate vein being shown clearly. However, cross sectional echocardiography in our patient with coexisting absent pulmonary valve syndrome did not show totally anomalous pulmonary venous connection to the coronary sinus. This patient died from severe respiratory complications and at necropsy very small pulmonary veins, again reflecting decreased pulmonary blood flow, were seen connecting to the coronary sinus.

This combination of anomalies thus represents a considerable diagnostic challenge to the clinician. There are considerable practical implications to the diagnosis. It would clearly be undesirable to perform palliative surgery to increase pulmonary blood flow if the pulmonary venous return was obstructed. Muster and coworkers described just such a case, in which fatal intractable pulmonary oedema developed after a Potts anastomosis, there being only a 1·5 mm aortopulmonary anastomosis at subsequent necropsy.[1] Despite a clinical picture of reduced pulmonary blood flow, important changes in pulmonary vasculature developed in our three year old patient with partially obstructed mixed drainage. This patient was referred from another hospital and no formal measurements of pulmonary vascular resistance had been made. None the less raised pulmonary artery diastolic pressure should raise the possibility of pulmonary vascular disease in such a patient. It would be impractical for all patients with tetralogy of Fallot to have cardiac catheterisation before palliative surgery, however. We suggest that angiography should be considered in patients when cross sectional echocardiography fails to demonstrate clearly the pulmonary venous connections.

Echocardiography is likely to be even less sensitive when there is partially anomalous pulmonary venous drainage. It is perhaps less important to establish the diagnosis before palliative surgery under these circumstances. It is more likely that one or two anomalously draining veins will be detected at the time of cardiac catheterisation and angiography before complete correction. Their clinical importance is limited, however. Complete correction without re-routing of the anomalous veins can be performed safely. While this will inevitably result in a degree of excess volume load to the right ventricle, the long term follow up in our older patients suggests that this has little effect on symptoms or functional state. Only one of our patients had a hemianomalous pulmonary venous connection (case 4). This patient had a scimitar syndrome with a hypoplastic right lung and pulmonary artery. Pulmonary blood flow and hence venous return was limited and so correction of tetralogy of Fallot without re-routing of the anomalous pulmonary veins was thought to be appropriate. In other patients where the pulmonary venous return from an entire lung may drain anomalously, attempts to restore drainage to the left atrium should probably be pursued.

When pulmonary venous drainage is totally anomalous it should be possible to perform a one-stage procedure with anastomosis of the pulmonary venous confluence to the left atrium at the time of complete correction. Successful one-stage correction has been previously reported[5,7,8] and the postoperative course in our patient was relatively uncomplicated. If the patient is unsuitable for complete correction, but requires palliative surgery to increase pulmonary blood flow, correction of the anomalous pulmonary venous return should be performed at the same time because of the risk of postoperative pulmonary oedema.[1]

Tetralogy of Fallot is rarely associated with anomalous pulmonary venous connection. The diagnosis is rarely suspected clinically because the reduction of pulmonary blood flow dominates the clinical presentation. The diagnosis may be made by cross sectional echocardiography, but angiography should be considered if normal pulmonary venous drainage cannot clearly be shown by non-invasive techniques. Complete correction with anastomosis of the pulmonary venous confluence to the left atrium is best performed within the first year of life if pulmonary venous connection is totally anomalous, particularly if there is any evidence of pulmonary venous obstruction. Correction of tetralogy of Fallot without re-routing of anomalously draining veins can be performed without serious long term sequelae if only one or two lobar vessels are affected.

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Diagnostic echocardiographic features of the sinus venosus defect

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Abstract

To establish the diagnostic criteria for a sinus venosus atrial septal defect cross sectional echocardiograms, cineangiograms, and surgical notes of all patients with this diagnosis seen at the Children's Hospital of Pittsburgh between 1986 and 1988 were reviewed. Seven patients were identified. In each the extent of the atrial septum and the nature of the junction of the superior vena cava with the atria were evaluated echocardiographically from the subcostal position. All had overriding of the superior vena cava and abnormally connected right pulmonary veins. Six patients had undergone cardiac catheterisation and cineangiography. Five patients underwent surgical repair. The operative findings were consistent with the expected morphology in all five, and these features were additionally confirmed in a specimen from the cardiopathological museum. Therefore, the basic anatomical feature of a superior sinus venosus interatrial communication is a biatrial connection of the superior vena cava. This, together with anomalous drainage of the right sided pulmonary veins, results in an interatrial communication outside the confines of the true atrial septum. Overriding of the superior vena cava across the upper rim of the oval fossa is suggested as the pathognomonic diagnostic feature that can clearly be demonstrated echocardiographically from the subcostal position. In essence the lesion is an interatrial communication rather than an atrial septal defect.

Interatrial communications are regarded as being among the simplest of congenital cardiac malformations; none the less, the echocardiographic distinction of the anatomical varieties has been far from certain. In morphological terms the key to diagnosis is that only those communications within the confines of the oval fossa are true "septal" defects.[1] Of the other malformations permitting an interatrial communication, the ostium primum defect is really an atrioventricular septal defect[2] whereas the rare coronary sinus defect is caused by unroofing of the course of the sinus through the left atrioventricular groove. The sinus venosus defect is the most difficult to identify. In 1907 the defect was recognised as overriding of the superior vena cava such that it achieved a biatrial connection[3]; later Swan *et al* suggested[4] that this was the consequence of persistence of venous connections between the right and left atria. Review of the anatomy confirms that, almost always, the important anatomical feature is biatrial connection of the superior vena cava which in effect produces an extraseptal interatrial conduit. With this morphology in mind, we examined the cross sectional echocardiographic features of those patients presenting recently at the Children's Hospital of Pittsburgh with a suspected diagnosis of the sinus venosus variant of interatrial communication.

Patients and methods

Since 1986, seven patients (four male and three female, aged 3–45 (median 4 years)) in whom a superior sinus venosus interatrial communication was diagnosed were evaluated by cross sectional echocardiography. In all patients the atrial septum and the junction between the superior vena cava and the atrial chambers had been carefully examined from the subcostal position with a Hewlett Packard 77020 sector scanner. Five of these patients have had cardiac catheterisation and four of these subsequently underwent surgical correction. One other patient (case 6) had surgery without previous cardiac catheterisation. The echocardiograms, angiograms, and surgical notes were reviewed. Two other patients were excluded when, on review, they were found to have left atrial isomerism. We also examined the single necropsy specimen in our cardiopathological museum with a sinus venosus interatrial communication.

Results

There is only one heart in the cardiopathological collection of the Children's Hospital of Pittsburgh that unequivocally shows the features of the sinus venosus interatrial communication. The major feature of this heart, which had undergone surgical repair, is an anomalous connection of the superior vena cava such that it connects directly to the roof of the left atrium in addition to having its anticipated right atrial connection along the terminal groove. As a consequence of this anomalous connection, the opening of the vein is equally committed to both right and left atria, overriding the rim of a normally formed oval fossa. The fossa itself was anatomically intact and the inferior vena cava and coronary sinus connected normally to the right atrium. Three right pulmonary veins, however, connected anomalously to the vena cava and its junction with the right atrium. Taken together, the anomalous venous connections formed an extensive interatrial communication outside the confines of the true atrial septum.

The table summarises the echocardiographic, cineangiographic, and surgical data of the seven patients. All seven patients examined echocardiographically showed an anomalous connection with the superior vena cava. This could be demonstrated only from the subcostal position. The arrangement is such that the superior vena cava overrides the atrial septum and there is a large interatrial communication (figure A). In all of them, the true atrial septum seemed to be intact, although Doppler evaluation showed patency of the oval fossa in two (cases 4 and 5). A right pulmonary vein was connected to the junction of the superior vena cava with the right atrium in all patients. An enlargement of the coronary sinus was noted in patients 1, 3, and 4, and the presence of a persistent left superior vena cava was suspected.

Five patients underwent cardiac catheterisation (cases 1, 2, 3, 5, and 7). Angiography clearly delineated the abnormal connection with the superior vena cava in only one patient (case 2) (figure B). The junction of the superior vena cava with the right atrium was not profiled in the other four. The oval fossa was patent in four patients. A persistent left superior vena cava draining to the coronary sinus was found in patients 1 and 3, in whom it was suspected echocardiographically. Absence of a brachiocephalic vein was shown by cineangiography but not by echocardiography. The right pulmonary venous connections were clearly displayed by cineangiography and were to the junction of the superior vena cava and the right atrium in all patients. Three patients had more than one pulmonary vein connection to this junction (cases 1, 2, and 5). One other patient (case 6) underwent surgical correction without prior cardiac catheterisation. In this patient one large and two small right sided pulmonary veins were found draining at the junction between the superior vena cava and the right atrium.

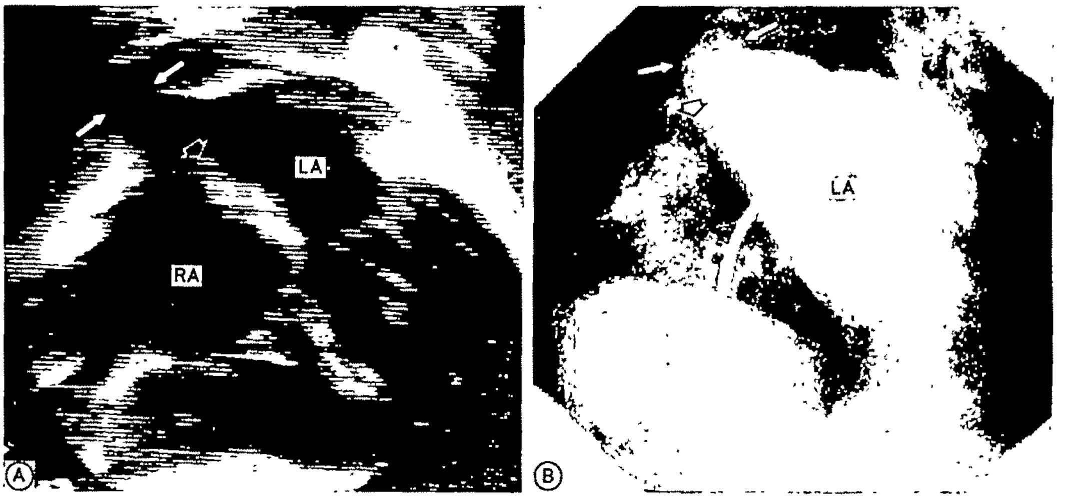
The operative note was consistent with the diagnosis of a sinus venosus interatrial communication in all five patients who had undergone surgical correction. In all the superior vena cava was overriding the superior limb of the oval fossa and had a biatrial connection.

Echocardiographic, cineangiographic, and surgical findings in sinus venosus interatrial communications

Patient		Echocardiography			Cineangiography			
		Connection			Connection			
No	Age (yr)	SVC	RPV	AA	SVC	RPV	AA	Surgery
1	5	O	SVC-RA	LSVC	U	2 SVC-RA	LSVC PFO	SVD
2	3	O	SVC-RA		O	2 SVC-RA	PFO	SVD
3	3	O	SVC-RA	LSVC	U	SVC-RA	LSVC PFO	SVD
4	6	O	SVC-RA	LSVC PFO				
5	4	O	SVC-RA	PFO	U	2 SVC-RA	PFO	SVD
6	45	O	SVC-RA					SVD
7	4	O	SVC-RA		U	SVC-RA		

AA, associated anomalies, LSVC, left superior vena cava draining to the coronary sinus; O, override, PFO, patent foramen ovale; RPV, right pulmonary vein, SVC-RA, superior vena cava-right atrial junction; SVC, superior vena cava; SVD, sinus venosus defect, U, unclear

(A) Cross sectional echocardiogram from the subcostal position (patient 2) showing a large interatrial communication with overriding of the superior vena cava (closed arrows). The atrial septum was intact. (B) Cineangiogram from the same patient with the catheter in the left atrium through a patent oval fossa showing the abnormal communication (closed arrows) between the superior vena cava and an intact atrial septum (open arrows) LA, left atrium; RA, right atrium.



Discussion

The difference between an atrial septal defect and an interatrial communication is crucial in the differentiation of the various congenital malformations that produce the potential for atrial shunting. Only the secundum atrial septal defect is a true hole within the confines of the atrial septum. The ostium primum defect is caused by a deficiency of the atrioventricular septum and is diagnosed because of the stigmata of atrioventricular septal defects.[5 6] Shunting through the rare coronary sinus defect occurs because of absence of the "common wall" that normally separates the sinus from the left atrium. It is, perhaps, the sinus venosus defect that is most difficult to understand and diagnose. Thus, in their echocardiographic study, Nasser and his colleagues state that the defect exists because "the atrial septum is deficient in its superior aspect".[7] When Abbott initially reviewed descriptions of the defect as long ago as 1907, she, too, pointed to the "high" location of the defect but, significantly, placed great emphasis on the biatrial connection of the superior vena cava.[3] It was Ross, in his review of the defect, who first highlighted its extraseptal location.[8] This was subsequently confirmed by Swan *et al*, who appropriately described the lesion as an interatrial communication rather than a septal defect.[4] This extraseptal location and the biatrial venous connection are the keys to both echocardiographic and surgical diagnosis. It was the biatrial venous connection that was the most obvious feature in our echograms, being present in all patients and better demonstrated by echocardiography than angiography. Disregard of this anatomical feature may account for the relatively low sensitivity in diagnosing this lesion in a recent study by cross sectional echocardiography with colour flow mapping.[9] Anomalous right pulmonary venous connections were better detected angiographically as was presence or absence of the left brachiocephalic vein in the presence of a persistent left superior vena cava.

The diagnostic anatomical and echocardiographic criterion for which we now search in the sinus venosus defect is the overriding of the superior vena cava. Because of its extraseptal location it is better to describe this lesion as an interatrial communication rather than an atrial septal defect. We believe that the lesion would be better understood if it were regarded as a defect of the superior vena cava.

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Coarctation of the aorta and post-stenotic aneurysm formation

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Abstract
Despite earlier angiography, post-stenotic aneurysm of the aorta was an unexpected finding at operation in two patients with coarctation. One aneurysm was found in an intercostal artery in a 19 year old man and the other was a false aneurysm just distal to the coarctation site in a 7 year old boy. These aneurysms are fragile, apt to rupture, and difficult to diagnose preoperatively. Though local factors such as jet streams and bacterial endocarditis may influence their formation there must be an underlying generalised weakness in the arterial wall.

A coarctation should not be regarded as an isolated arterial abnormality because it may be a feature of a more generalised disease. Because of the risk of rupture, which may not be prevented by antihypertensive treatment, operation should not be delayed in any age group.

Coarctation of the aorta is one of the most common congenital cardiac abnormalities, occurring in about 1 in 1200 live births. In untreated patients the average life expectancy (from one series of 200) was 32 years,[1] with the cause of death (according to Campbell[2]) being cardiac failure (25·5%), endocarditis (18%), cerebrovascular haemorrhages (11·5%), "aortic" rupture (21%), and unknown reasons (24%).

The association of aneurysms with coarctation of the aorta is well recognised. In a series of 1091 patients reviewed in 1960, Skandalakis *et al* reported 102 aneurysms of which 63 were distal to the coarctation with 12 in the intercostal arteries.[3] It is important to detect such aneurysms because rupture was the cause of death in 76% of patients with aneurysms. Although computed tomography may be helpful, angiography remains the mainstay of diagnosis, yet even with this, aneurysms are often discovered only at operation. Though the development of aneurysms proximal to the coarctation might be expected (because of hypertension in the upper part of the body), aneurysms are equally common distal to the coarctation site and are just as likely to rupture. We present two such cases and discuss the possible mechanisms leading to aneurysm formation.

Case reports

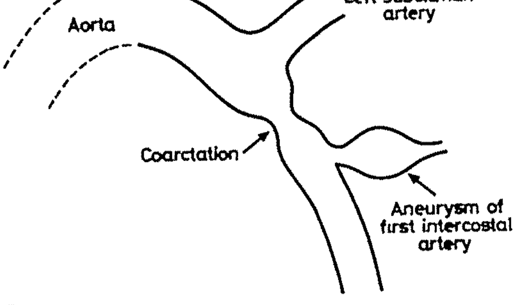
CASE 1

A 19 year old man was referred to us in April 1989 after a routine medical examination when he was found to have hypertension with a blood pressure of 170/110 mm Hg in the right arm, no femoral pulses, and a systolic bruit. On questioning he complained of a reduced exercise tolerance, claudication in both legs, and slight breathlessness on exertion. An electrocardiogram showed sinus rhythm with evidence of minimal left ventricular hypertrophy. Echocardiography and angiography confirmed left ventricular hypertrophy with good left ventricular function, but also a coarctation of the aorta with normal distal arteries.

Treatment with atenolol was started while he awaited operation. At operation a post-ductal coarctation was found. This was resected and a gelatin impregnated knitted Dacron graft (Vascutek, Inchinnan, Scotland) was sutured into place to restore aortic continuity. In addition to the coarctation, however, a 1 × 1 cm aneurysm of the first left intercostal artery was found. This was very thin walled and at risk of rupture, with the dilated portion starting 0·5 cm away from an aortic ostium of normal size (figure). The intercostal artery was transected proximally and ligated distally and the aortic ostium oversewn. He made a good recovery postoperatively and was well at follow up 7 months later though treatment with atenolol was continued.

CASE 2

A 7 year old boy presented to us in 1983 with a history of claudication in both legs when running and of becoming easily fatigued. On examination he was found to be hypertensive with a blood pressure of 150/90 mm Hg in the right arm, no femoral pulses, and a systolic murmur at the left sternal edge. An electrocardiogram was unremarkable but angiography showed a coarctation of the aorta and mild aortic incompetence. At operation the coarctation was confirmed and was repaired



Drawing showing coarctation of the aorta and the aneurysm of the first intercostal artery in case 1.

by widening the aorta with a diamond shaped Dacron patch. A 2 cm false aneurysm of the aorta was also found 3 cm distal to the coarctation. Over most of the circumference the wall consisted only of adventitia, and the aneurysm was repaired with Teflon buttressed sutures and reinforced by a Teflon collar around the aorta with an internal diameter of 2·5–3 cm. Postoperative recovery was uneventful and 6 years later he remained well, normotensive, and on no medication.

Discussion

Coarctation of the aorta is usually repaired before the age of 5 years because of the increasing risk of irreversible hypertension and left ventricular hypertrophy developing when repair is delayed.[4] An equally serious and potentially fatal complication of a coarctation, but one that is less well appreciated, is aneurysm formation. Aneurysms may be single or multiple and may occur in the aorta, intercostal arteries, Abbott's artery, or the cerebral vessels. Apart from the risk of rupture (that may lead to sudden death) or a cerebrovascular accident, pressure on the anterior spinal artery or the spinal cord from an intercostal artery aneurysm can also lead to paralysis.[5]

The existence of so many arterial abnormalities suggests that a coarctation may be a feature of a more generalised arterial disease rather than a discrete entity. Bicuspid aortic valves are, for example, a frequent association.[1]

The cause of aneurysm formation is unclear but in the upper part of the body hypertension is a possibility. There is some evidence that coarctectomy does not protect against hypertension if the operation is delayed beyond the first few years of life and hypertension has been uncontrolled.[4] None the less, the pressure required to produce medial dissection is likely to be far greater than aortic blood pressure, even in cases of severe hypertension.[6,7] This implies that for an aneurysm to develop there must also be some congenital weakness in the arterial wall. The finding that only 32% aneurysms were proximal to the coarctation in one large series[3] is further evidence against the role of hypertension.

In our two cases aneurysms developed on the "low flow" side of the coarctation and therefore hypertension was clearly not the cause. A role has been suggested for bacterial endocarditis,[8] which is undoubtedly important in some cases, perhaps aided by eddy currents in low flow areas. One further possibility is that some post-stenotic aneurysms may be directly attributable to jet streams of blood coming through the narrowed segment and impinging on the distal aortic wall. Skandalakis *et al* suggested that this might have accounted for 6% of coarctations in their series[3]; it was probably the cause of the false aneurysm in our patient 2. Nevertheless, a congenital weakness in the structure or biochemistry of the artery wall may well account for most cases. When aneurysms arise in the region of the ligamentum arteriosum it is possible that ductal tissue could become incorporated into the aortic wall during development, so as to produce a local weak spot. The more widespread appearance of aneurysms may be explained by the evidence that there is destruction of elastic tissue in the tunica media of the arterial wall together with an alteration in the mucopolysaccharide protein matrix.[7] With this background, hypertension or post-stenotic jet streams may then be compounding factors. In case 1, however, the intercostal aneurysm was on the low flow side of the coarctation and arose some distance away from the aorta and the coarctation site; so it is unlikely that either factor was operating. In contrast, the false aneurysm in case 2 may well have been caused by abnormal stress on the aortic wall from a jet stream. Certainly it is unusual for an aneurysm to develop in such a young patient.

There is no doubt that there is a strong association between coarctation of the aorta and aneurysm formation. Though to date there has only been one definite report of rupture of an aneurysm of an intercostal artery[9] (perhaps because these are misreported as aortic ruptures) there is no doubt that aneurysms distal to the coarctation are common and are potential sites of rupture. Both our patients underwent preoperative angiography but this did not detect the aneurysms, both of which were about to rupture. These fragile, thin walled lesions are often found unexpectedly at operation, and they do not tolerate manipulation during coarctation repair.[4,9] Once detected, coarctation of the aorta should be operated upon without delay—in adults and older children just as in neonates—because of the potentially fatal consequences of rupture of an unsuspected aneurysm. It is unwise to maintain such patients on antihypertensive treatment and defer operation. Though thoracic aneurysms will be detected and can be dealt with at the time of coarctation repair, associated cerebral aneurysms are likely to be clinically silent and will remain undetected. Because 30–50% of patients operated on in late childhood or adulthood remain hypertensive after operation[4] and because coarctectomy itself will not protect against rupture, it is important to provide long term antihypertensive treatment.[10]

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CASE REPORTS

Supravalvar aortic stenosis: a complication of aortic valve surgery

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Abstract
After a patient had aortic valvotomy and aortotomy for the relief of valvar aortic stenosis supravalvar stenosis developed over the next six years.

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Case report

A 3 month old boy had the morphological and developmental features of cretinism and was found to have congenital hypothyroidism. He rapidly improved when he was treated with thyroxine. He had a systolic murmur. When he was 5 years old his electrocardiogram showed changes consistent with left ventricular hypertrophy and his chest *x* ray showed cardiac enlargement. He underwent cardiac catheterisation and angiography (figure) and was found to have valvar aortic stenosis with a peak systolic withdrawal gradient of 85–100 mm Hg. Under cardiopulmonary bypass a 1 cm incision was made in the aorta. The aortic valve commissures were fibrosed and thickened and an aortic valvotomy was performed without complication.

After operation he remained well but with residual signs of left ventricular outflow obstruction and evidence of left ventricular hypertrophy on his electrocardiogram. Because of the development of breathlessness at the age of 12 years repeat operation was considered. At this time he was in sinus rhythm with a blood pressure of 110/75 mm Hg and a sustained apical impulse. On auscultation there was an ejection sound in the second right intercostal space and an ejection systolic murmur (grade 4/6) together with an early diastolic murmur at the left sternal edge. The cardiac diameter was at the upper limit of normal on plain chest *x* ray and his electrocardiogram showed evidence of left ventricular hypertrophy. Cardiac catheterisation was not carried out again and he was referred directly for further operation.

Angiogram before first operation.

At operation cardiopulmonary bypass was established. The pericardial cavity was obliterated by firm adhesions and the left ventricle was massively enlarged. There was a thrill over the ascending aorta but no post-stenotic dilatation. The pulmonary artery and right ventricle were normal. The aorta was opened with a long oblique incision and the aortic valve examined. This was bicuspid with fusion of the right coronary and non-coronary cusps. Unexpectedly there was a supravalvar stenosis with a shelf above the left coronary cusp approximating the two commissures of that cusp to each other and overhanging the left coronary orifice. The internal diameter of the stenosis measured 1 cm. The aortic incision was extended beyond the supravalvar stenosis and the fibrous shelf was excised. The aortic valve was replaced with a fresh homograft and a dacron gusset was inserted into the aortic root.

He made a good postoperative recovery with gradual regression of the electrocardiographic abnormalities. He still had a soft ejection systolic and an early diastolic murmur at the left sternal edge. Echocardiography 4 years later showed that the left ventricle was normal without hypertrophy or dilatation, and with good systolic function. The aortic cusps seemed to be normal. An indirect carotid pulse tracing showed a normal left ventricular ejection time. Cardiac catheterisation 5 years after operation showed a normally contracting left ventricle and mild to moderate aortic regurgitation on the aortogram. Fifteen years later his left ventricular ejection time was still normal and Doppler echocardiographic studies 18 years after operation showed a maximum gradient of 18 mm Hg across the aortic valve, trivial aortic regurgitation, and no evidence of supravalvar stenosis.

Discussion

Supravalvar aortic stenosis was first described by Mencarelli in 1930.[1] In the 1950s the first preoperative diagnosis was described and the first surgical repair documented.[2] The association of supravalvar aortic stenosis with an elfin-like facies and infantile hypercalcaemia (Williams's syndrome) is well known but there are also descriptions of familial and sporadic cases of supravalvar stenosis without the other characteristics associated with Williams's syndrome.[3] Our patient had none of the features suggestive of Williams's syndrome and his serum calcium concentration was normal.

Our patient was congenitally hypothyroid but an association between hypothyroidism and supravalvar aortic stenosis has not been described. Hutchins *et al* described a case of parafollicular cell (C cell) hyperplasia in a patient with supravalvar stenosis and suggested that C cell hyperplasia occurs in response to persistent hypercalcaemia and that thyrocalcitonin function is augmented rather than impaired.[4] Despite the location of C cells within the thyroid gland we have not found any reports describing an association between supravalvar aortic stenosis and thyroid dysfunction.

Whatever the possible associations leading to supravalvar aortic stenosis, we have no evidence that this patient had supravalvar aortic stenosis before the first operation on the aortic valve. Although supravalvar aortic stenosis is often found in association with aortic valve abnormalities, review of the original angiogram before the first operation (figure) did not suggest either supravalvar obstruction or aortic hypoplasia. Nor was there any suggestion at the time of the first operation that the patient had supravalvar aortic stenosis. Morrow *et al* in a review of 43 cases of supravalvar aortic stenosis found 13 with associated abnormalities of the aortic valve.[5] Somerville and Ross described an unusual type of aortic valve stenosis associated with supra-aortic stenosis[6]: the valve was grossly thickened and lumpy and the supra-aortic stenosis was associated with aortic hypoplasia. The appearance of the aortic valve in our patient did not accord with Somerville and Ross's description nor was the aorta hypoplastic. The description of the supravalvar aortic stenosis in our patient was best described as "hourglass" rather than "membranous" or "hypoplastic".

We consequently do not believe that our patient had congenital supravalvar aortic stenosis but that the lesion was the result of local trauma at the time of the first operation and developed over the next 6 years.

We thank Professor M Yacoub for allowing us to report this case on whom he operated and Dr M Raphael for his advice on the original angiogram.

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Aortic atresia: survival to adulthood without surgery

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Abstract

Aortic atresia is a rare congenital cardiac defect. It usually leads to death in the neonatal period. A patient with aortic atresia has survived to the age of 24 years without any surgical procedure. In view of the uncertain results of reconstructive surgery this case may have therapeutic implications.

Aortic atresia is a rare congenital cardiac defect that is usually associated with the hypoplastic left heart syndrome and is fatal in the newborn. Surgical techniques can prolong life.[1] We report survival to adult life without surgery of a patient with aortic atresia.

Case report

The patient, a man aged 24, has aortic atresia with a normal sized left ventricle, a large ventricular septal defect, and a patent ductus arteriosus.

He was the product of a normal pregnancy with no family history of congenital heart disease. After birth he briefly required oxygen for cyanosis. No abnormalities were detected at this time and he left hospital after the normal postnatal period. When he was a month old he was admitted to The Hospital for Sick Children, Great Ormond Street, with chronic feeding difficulties. He was not cyanosed but was reported to have heart failure with intercostal recession with an electrocardiogram showing left ventricular hypertrophy and cardiomegaly with plethoric lung fields on the chest radiograph. Cardiac catheterisation showed contrast passing into the minute ascending aorta via a patent duct. The left atrium and left ventricle were of normal dimensions with the left ventricle emptying into a huge pulmonary artery through a large ventricular septal defect. The table shows the oxygen saturations and pressures recorded. Treatment with digoxin and diuretics was started and he improved. By the age of one year he had become cyanosed. When he was five years old he had a poor exercise tolerance, frequent respiratory tract infections, and established clubbing of the fingers with central cyanosis. Cardiac catheterisation showed features of the Eisenmenger syndrome (table).

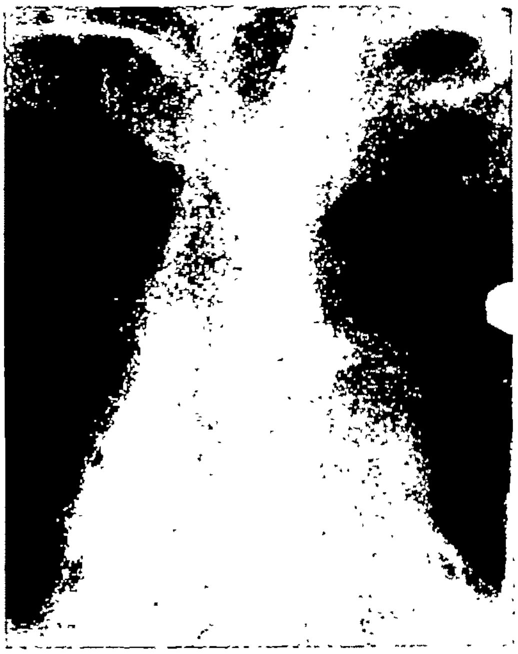
He was referred to the National Heart Hospital at the age of 15. He was more cyanosed and the haemoglobin concentration was 230 g/l. In view of the polycythaemia, regular venesection with volume replacement was started. The chest *x* ray showed moderate cardiomegaly, enlargement of the proximal pulmonary arteries, and oligaemic lung fields. Electrocardiography showed right atrial and biventricular hypertrophy. Cardiac catheterisation showed that there was no flow across the aortic valve and that oxygen saturation was identical in the pulmonary artery and abdominal aorta (table). The figure shows the hypoplastic aortic root and the coronary arteries, which were perfused retrogradely from the patent duct.

Now aged 24 he has signs of pulmonary hypertension and incompetence with deep cyanosis. His fingers and toes are equally clubbed. He has recurrent small haemoptyses. He works full time and has moderate limitation from dyspnoea (ability index 2). Heart-lung transplantation will be considered when he becomes more limited; a long transverse anastomosis with the donor arch will be required.

Data from cardiac catheterisation at three different ages

	4 weeks			*5 years*		*15 years*	
Chamber	*Pressure (mm Hg)*	*Oxygen sat (%)*		*Pressure (mm Hg)*	*Oxygen sat (%)*	*Pressure (mm Hg)*	*Oxygen sat (%)*
Superior vena cava				64		64	
Right atrium	Mean = 3		60	Mean = 4	64	Mean = 4	68
Right ventricle	105/0	*Apex*	80	90/10	76	125/5	67
		Inflow	46				
		Mid	62				
		High	86				
Pulmonary artery	110/55*		90*	90/70	87	100/75	87
Left atrium	Mean 17		95				
Left ventricle						110/10	95
Aorta	70/45*		98*	90/65	88	100/70	88

*These readings in the aorta were not simultaneous with those in the pulmonary artery. Presumably simultaneous readings would have given the same value in both, as in the later studies.



Angiogram (anterior-posterior view with caudal tilt) at 15. The catheter is in the aortic arch, inserted via the right brachial artery. Contrast is seen filling the ascending aorta, which is hypoplastic, and the coronary arteries.

Discussion

Aortic atresia is a feature of "hypoplasia of the aortic tract complexes".[2] Most cases have associated left ventricular hypoplasia and mitral atresia so they are grouped within the "hypoplastic left heart syndrome".[3] In our patient, however, there was a normal left ventricle, which has been reported in 4% of cases.[4 5] This occurs when there is no reduction of inflow (mitral atresia or stenosis). The outlook for those with a normal and those with hypoplastic left ventricles, however, was much the same, with a mean age at death of five days. The longest survival in these necropsy series was 56 days. The longest previously reported survival of any child with aortic atresia is three years.[6]

Why has our patient survived for so long? The anatomy of the heart was favourable in three ways. Firstly, he is one of the few patients with aortic atresia who has a normal left ventricle. Secondly, his ventricular septal defect was large enough not to restrict outflow from the left ventricle. Thirdly, in the neonatal period he had a large ductus arteriosus. It was essential that this should stay patent, and it did. In addition, there was no coarctation of the aorta.

Presumably pulmonary vascular resistance was relatively low initially, permitting a high pulmonary blood flow. This allowed good oxygenation, but also caused pulmonary congestion. This initial situation clearly permitted survival beyond infancy. The function of the left ventricle did not deteriorate because its outflow, via the ventricular septal defect, was not restricted. Since infancy the pulmonary vascular resistance has increased, pulmonary blood flow has fallen, and the coronary arteries are perfused retrogradely with blue blood. The patient thus lives on as a case of the Eisenmenger reaction. Such patients (with different cardiac anatomy) have survived into the sixth decade.

It seems that in cases of aortic atresia with a large ventricular septal defect and normal left ventricle, medical attention in infancy might best be directed at keeping the pulmonary vascular resistance high and the duct permanently open by pharmacological treatment. This could be as effective as reconstructive surgery in prolonging life, or even more effective, and cause considerably less suffering, risk, and expense. Also, avoidance of a thoracotomy would improve the chances of successful heart-lung transplantation later in life.

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Restoration of sinus rhythm during two consecutive pregnancies in a woman with congenital complete heart block

Diana R Holdright, G C Sutton

Abstract

In a woman with congenital complete heart block atrioventricular conduction was normal during two successive pregnancies. Pregnancy, labour, and delivery were uncomplicated on both occasions and complete heart block returned post partum.

Successful pregnancies have been reported in many patients with congenital complete heart block.[1-3] The restoration of normal atrioventricular conduction during pregnancy in a patient with congenital complete heart block is unusual, however. We report a patient in whom atrioventricular conduction became normal during two successive pregnancies, while complete heart block was the predominant rhythm when the patient was not pregnant.

Case report

A Cypriot woman had been found coincidentally to have complete heart block at the age of 10 years, but was not informed of this until some years later. She was assessed for the first time at the age of 21. At that time she was aware of heart rate changes, particularly when the rate increased, and she was occasionally dizzy when her rate fell below 40 beats/minute; she had never had any syncopal episodes. She had no significant illness in her life and there was no relevant family history. She was not receiving any medication.

Apart from bradycardia of 50 beats/minute examination was unremarkable. Review of her electrocardiograms showed that at the age of 10 years she had complete atrioventricular block with normal QRST-T complexes and a ventricular rate of 42 beats/minute. Subsequent electrocardiograms showed sinus rhythm with a normal PR interval (aged 17 years), first degree heart block (PR interval of 0·22 s) (aged 21 years), and advanced second degree atrioventricular block (aged 23 years). Holter monitoring when she was 21 showed episodes of sinus tachycardia (130 beats/minute) and nocturnal complete heart block. Her chest *x* ray and an echocardiogram were normal.

In 1986, when she became pregnant for the first time she had normal atrioventricular conduction with a long PR interval (0·2–0·24 s). Holter monitoring at 32 weeks of pregnancy showed occasional periods of complete heart block with no specific diurnal pattern. Labour was spontaneous and during the second stage sinus tachycardia developed with a ventricular rate of 120 beats/minute. She had an uncomplicated delivery and post partum complete heart block returned. In 1988 she became pregnant for the second time, and again atrioventricular conduction became normal with a PR interval of 0·2 s. Her pregnancy was unremarkable and she had a sinus tachycardia during delivery. Almost immediately after delivery she returned to complete heart block alternating with advanced second degree atrioventricular block.

A month after the second pregnancy an exercise test was performed and she managed 9 minutes of the Bruce protocol, stopping because of breathlessness. Her resting ventricular rate was 60 beats/minute with a PR interval of 0·24 s. Her resting blood pressure was 110/65 mm Hg. At peak exercise the ventricular rate was 140 beats/minute, the PR interval was unchanged, and the systolic blood pressure was 130 mm Hg. Two minutes into recovery a 2:1 second degree atrioventricular block developed with a ventricular rate of 60 beats/minute.

Discussion

Congenital complete heart block was first described by Morquio in 1901.[4] The diagnosis is made if the criteria established by Yater[5] are fulfilled—heart block must be demonstrated electrocardiographically and a slow pulse ascertained at an early age; there must be no history of infection such as diphtheria or rheumatic fever and no evidence of ischaemic heart disease or other cardiomyopathy, nor a history of previous cardiac surgery. The incidence is approximately 1 in 15 000 to 22 000 live births[6 7] and, unlike acquired complete heart block, the QRS complex is usually narrow.

The ventricular response to exercise is generally more pronounced than in acquired complete heart block. In our patient, albeit one month post partum, sinus tachycardia with a constant PR interval developed during an exercise test but two minutes after maximum tolerated work load a 2:1 second degree atrioventricular block supervened.

Complete heart block has been shown to disappear in some patients, with sinus rhythm being restored sometimes for several years.[8] This is more common in congenital than acquired complete heart block. Indeed some patients change constantly between first, second, and third degree heart block—that is incomplete complete heart block. Even before pregnancy our patient had documented

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episodes of sinus rhythm in 1975, 1977, and 1981.

Many successful pregnancies have been reported in patients with congenital heart block but Adams-Stokes attacks may develop during delivery. This may be precipitated in part by the Valsalva manoeuvre which slows the ventricular rate. Esscher described pregnancies in 12 women with congenital heart block.[1] Ten patients had 19 pregnancies with no complications while in two patients Adams-Stokes attacks developed during three pregnancies. The development and maintenance of sinus tachycardia during delivery reduced the likelihood of a syncopal episode in our patient.

We speculate that the hormonal changes of pregnancy—with increased production of oestrogens, progesterone, and corticosteroids[9]—may have improved atrioventricular conduction in our patient. It has long been recognised that steroids can improve atrioventricular conduction. In 1955 Lown *et al* showed that the PR interval was longer in Addison's disease and shorter in Cushing's syndrome than in healthy individuals.[10] Hormone replacement treatment improved atrioventricular conduction in those patients with Addison's disease. Patients with Cushing's syndrome had either a short PR interval or a normal PR interval. In general, those patients with a short PR interval had adrenal cortical hyperplasia and urinary excretion of 17-ketosteroids (an indicator of adrenal cortical function) that was four times higher than that in the group with a normal PR interval who at surgery were found to have adrenal adenomas.

There is a well recognised association between maternal systemic lupus erythematosus and complete heart block developing in utero. The conduction tissue damage in utero does not continue in adult life, however. Thus it seems improbable that the hormonal changes of pregnancy could have mitigated the effects of lupus in our patient, who in any case had no overt clinical features suggestive of lupus erythematosus (specific serological testing was not performed). Alternatively, rather than producing structural changes in the conducting tissues, steroids might produce their effect by altering the intracellular-extracellular balance of electrolytes, in particular producing a net shift of potassium out of cells. Improved atrioventricular conduction in patients with complete heart block treated with chlorothiazide[11] was associated with a fall in extracellular potassium.

It is not known whether or not oestrogens or progesterone could have an effect on atrioventricular conduction; there are no published studies.

It is likely that the hormonal changes of pregnancy encouraged the restoration of sinus rhythm in our patient. This improvement in atrioventricular conduction might indicate a better prognosis than in those patients in whom complete atrioventricular block persists during pregnancy.

We thank Dr E Rowland for his advice and Mr C Wright who delivered the patient of her two children.

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Eustachian valve endocarditis

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Abstract

M mode and cross sectional echocardiography showed a highly mobile globular pedunculated mass (3·0 cm long with a maximum diameter of 1·5 cm) attached to the eustachian valve in a heroin addict with staphylococcal endocarditis.

Infective endocarditis in drug misusers was first reported in the 1930s.[1] Since then, right sided infective endocarditis has become much commoner.[2–4] Vegetations are the hallmark of endocarditis. In 1973 Dillon *et al* reported the first demonstration by echocardiography of valvar vegetations.[5] The echocardiographic findings in right sided endocarditis have been widely described.[6–8] We report the M mode and cross sectional echocardiographic findings in a patient with a vegetation of the eustachian valve.

Case report

A 23 year old male heroin addict was admitted to hospital with chills, malaise, right pleuritic chest pain, and fever. On physical examination blood pressure was 120/70 mm Hg, pulse 100 beats/min, respiratory rate 20/min, and temperature 38·8°C. The conjunctivae and the optical fundi were normal. There was no jugular venous distension. Fine rales were heard over the right lung base. Cardiac examination showed a normal sized heart. The first heart sound was normal and the second sound was split physiologically. Neither the liver nor the spleen was palpable. There were no petechiae, splinter haemorrhages, or Osler nodes. The haemoglobin concentration was 128 g/l and the white cell count was 15·8 × 10^9/l with a shift to the left. *Staphylococcus aureus* was given in six consecutive blood cultures. A chest *x* ray film showed right nodular densities consistent with septic pulmonary emboli. An electrocardiogram showed sinus tachycardia. The M mode and cross sectional echocardiograms showed evidence of a highly mobile mass (3·0 cm long and with a maximum diameter of 1·5 cm) that was globular and pedunculated and attached to the eustachian valve (figs 1 and 2). The other cardiac valves were normal.

Staphylococcal endocarditis affecting the eustachian valve was diagnosed and the patient was treated with oxacillin and gentamicin for 6 weeks. The pleuritic chest pain present on admission disappeared by the fifth hospital day. The fever, leucocytosis, and the radiographic signs of lung disease resolved.

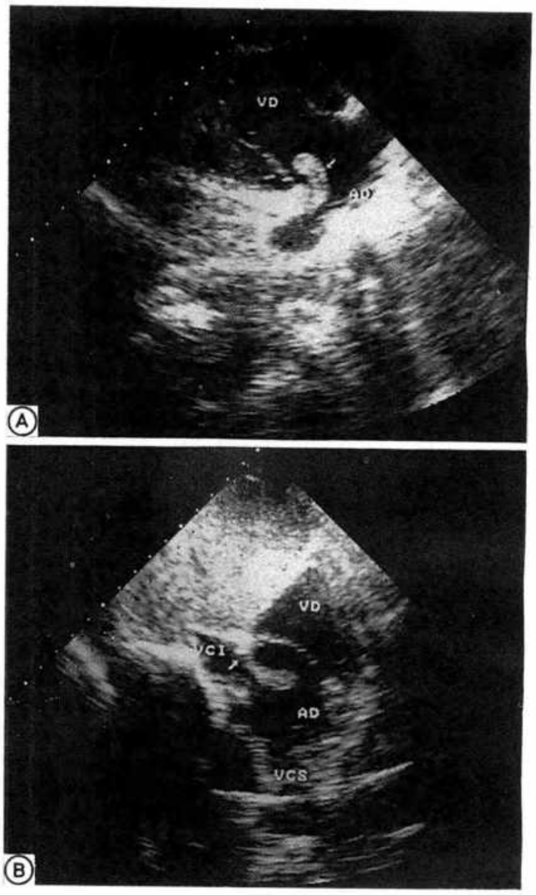

Figure 1 (A) Cross sectional echocardiogram in the parasternal view showing the right ventricular inflow tract. A large, pedunculated mass (arrow) projected into the right atrium (AD) from the junction of the inferior vena cava and the right atrium. VD, right ventricle. (B) Cross sectional echocardiogram in the subcostal view and sagittal projection. A pedunculated mass hung from the eustachian valve (arrow). VCI, inferior vena cava; VCS, superior vena cava.

A repeat cross sectional echocardiographic study before discharge again showed the vegetation, which seemed to be smaller. On re-evaluation five months later, the patient was symptom free; the vegetation persisted at the same site but was smaller than before.

Discussion

The eustachian valve or valve of the inferior vena cava is a normal remnant of the right valve of the sinus venosus. In the embryo this valve directs blood from the inferior vena cava into the left atrium through the foramen ovale.[9] Its

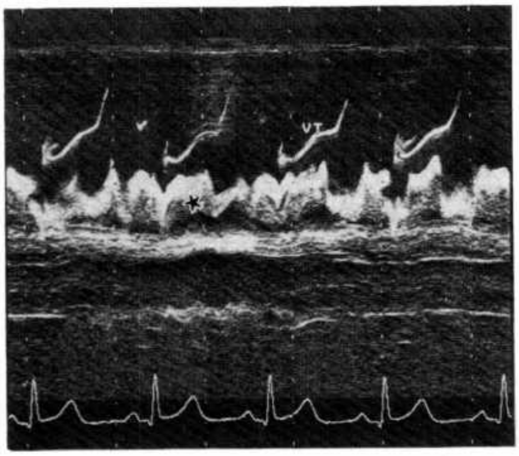

Figure 2 M-mode echocardiogram of the right ventricular inflow tract showing an abnorma cluster of dense, highly mobile and shaggy echoes (*) within the right atrium. The tricuspid valve (VT) appeared to be normal.

persistence may create or simulate cardiac disease.[10-12] The anatomical and echocardiographic features of this valve have been described.[13 14] Successful management of bacterial endocarditis depends on early recognition and prompt treatment. In right sided endocarditis there are often no definitive auscultatory findings and this makes diagnosis difficult. Echocardiography is an established non-invasive technique for detecting vegetations, haemodynamic sequelae, and other complications in patients with infective endocarditis.[15-18]

Edwards *et al* also reported a patient with eustachian valve endocarditis.[19] Unfortunately in their patient the eustachian valve was not specifically sought during the echocardiographic examination. Although surgical or pathological confirmation was not available in our patient, the triad of heroin addiction, staphylococcal septicaemia, and pulmonary infarction without evidence of peripheral venous disease supported the diagnosis of eustachian valve endocarditis.

Necropsy studies of patients with right sided infective endocarditis and of opiate addicts showed that the affected valves were nearly always anatomically normal before the onset of the cardiac infection, which was usually caused by highly virulent organisms, especially *Staphylococcus aureus*.[8] Vegetations associated with right sided endocarditis tend to be large.[17] Echocardiographically confirmed large vegetations do not usually disappear after medical treatment. All these features were seen in our patient.

Our patient and that of Edwards *et al* suggest that when bacterial endocarditis is suspected, especially in intravenous drug misusers, the eustachian valve should be echocardiographically examined for vegetations.

We thank Marcy Ashburn for her technical assistance.

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TECHNOLOGY

Balloon dilatation of the mitral valve by a single bifoil (2 × 19 mm) or trefoil (3 × 15 mm) catheter

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Abstract

The efficacy of balloon dilatation of the mitral valve by a bifoil (2 × 19 mm) or trefoil (3 × 15 mm) catheter (single catheter technique) was assessed in 53 patients (mean age 28) with mitral stenosis, most of whom were women. The procedure was unsuccessful in three patients. After balloon dilatation the left atrial pressure decreased from 22 mm Hg to 13 mm Hg and the mitral valve gradient from 12 mm Hg to 4 mm Hg. The mitral valve area increased from 0·7 cm^2 to 2·1 cm^2. Exercise time on the standard Bruce protocol increased from 3·9 minutes to 7·2 minutes. In 22 (44%) patients mitral regurgitation developed or the grade of regurgitation increased. Left to right shunts with pulmonary to systemic flow ratios > 1:5 were detected in four patients. Transient cerebrovascular episodes developed in two patients. One patient died after emergency valve replacement for severe mitral regurgitation.

Balloon dilatation of the mitral valve by the single catheter technique with the bifoil or trefoil catheters is an effective treatment for patients with mitral stenosis. Mild mitral regurgitation is a frequent complication of the procedure.

Since Inoue *et al*'s first description in 1984,[1] percutaneous balloon dilatation of the mitral valve has emerged as a new form of treatment for mitral stenosis. Dilatation with single[2] and double balloon techniques has been described.[3–5] The double balloon technique was more effective in dilating stenotic mitral valves than the monofoil single catheter technique.[6 7] The smaller (3 × 12 mm) trefoil catheter was used as part of the double balloon technique.[8] But we found little information on the use of a single catheter technique with bifoil or trefoil balloons for dilatation.[9] The catheter consists of two (bifoil) or three (trefoil) identical balloons mounted in parallel on a single 12F catheter. The balloons fill simultaneously when filled with saline.

The criteria, especially anatomical, for patient selection have received scant attention. We report our experience of balloon dilatation of the mitral valve by a bifoil or trefoil catheter in 50 patients with mitral stenosis. We also studied the effect of various clinical, haemodynamic, and echocardiographic variables on the outcome of the procedure and on the development of mitral regurgitation.

Patients and methods

PATIENTS

From May 1988 to June 1989 balloon dilatation of the mitral valve was attempted in 53 patients with symptomatic (New York Heart Association class II–IV) pliable isolated mitral stenosis (table 1). We excluded those with active rheumatic carditis, extensive calcification, severe subvalvar disease, and more than mild mitral or aortic regurgitation. Technical reasons related to transseptal catheterisation prevented valve dilatation in two patients. In one patient the mitral valve could not be split despite repeated inflations. The final study group consisted of 50 patients of whom 41 were women and nine men (mean age 28 years (range 15–50)). Forty six were in sinus rhythm and four had atrial fibrillation. Sixteen patients had trivial (1+) and two mild (2+) mitral regurgitation. Fourteen patients also had mild aortic regurgitation. Ten patients had mitral restenosis after having had closed mitral commissurotomy 4–13 years before. Nineteen patients were in New York Heart Association class II, 30 in class III, and one in class IV. Fluoroscopy showed mild mitral valve calcification in 13 patients.

ECHOCARDIOGRAPHY

Cross sectional echocardiography was performed in all patients before and after the procedure. The structure of the mitral valve was examined for leaflet mobility, leaflet thickening, subvalvar disease, and calcification; a score was obtained for each valve as described previously.[10] Out of a possible score of 16 (for a severely fibrotic valve with important subvalvar disease and calcification) the severity ranged from 3 to 9 (mean 5 3). This accords with our clinical findings that all patients had pliable mitral stenosis.

EXERCISE TREADMILL PERFORMANCE

All patients except one (New York Heart Association class IV) underwent symptom limited treadmill exercise (standard Bruce protocol) before and after (within one week) the

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Table 1 *Echocardiographic and haemodynamic characteristics of patients*

					MVA (cm²)	
Case	*Sex*	*Age*	*CMV*	*Echo score*	*Pre*	*Post*
1	F	29	–	3	0·9	3·9
2	F	29	–	8	0·7	1·5
3	F	47	–	6	0·7	2·1
4	M	15	–	7	0·3	1·0
5	F	17	–	5	0·5	3·2
6	M	35	+	7	0·9	4·7
7	F	27	–	7	0·6	1·7
8	F	26	–	4	0·4	2·7
9	F	28	–	5	0·5	1·1
10	M	20	–	9	0·3	—
11	M	23	–	7	0·4	2·4
12	F	15	–	4	0·5	1·8
13	F	36	–	5	1·0	2·7
14	F	20	–	6	1·1	2·7
15	F	23	–	5	0·8	1·8
16	F	43	+	6	1·2	3·5
17	M	28	–	6	0·9	2·7
18	F	22	–	3	0·8	1·8
19	F	37	–	4	0·4	2·6
20	F	46	–	4	0·5	1·3
21	F	23	+	7	1·1	2·2
22	F	49	+	5	1·4	2·2
23	F	18	–	4	0·7	2·1
24	F	27	–	4	1·0	2·0
25	F	34	–	6	0·7	1·2
26	F	44	–	5	0·6	1·5
27	F	24	–	5	0·6	1·9
28	F	24	–	3	1·3	2·1
29	F	27	+	3	0·6	1·4
30	F	21	–	6	0·6	1·1
31	F	38	–	5	1·2	2·8
32	F	22	–	4	0·6	2·4
33	F	46	+	6	0·9	3·3
34	M	27	–	4	0·8	2·1
35	F	18	–	5	0·5	1·0
36	F	18	–	7	0·6	1·0
37	F	42	+	8	0·9	1·9
38	F	16	–	4	0·6	1·6
39	F	21	–	5	0·7	1·6
40	F	50	–	7	1·5	3·1
41	F	26	–	5	0·4	2·3
42	F	25	–	8	0·7	1·5
43	M	32	–	5	0·7	3·5
44	F	33	+	7	0·8	1·6
45	F	36	+	5	0·9	2·8
46	M	36	–	7	1·2	2·0
47	F	17	+	6	0·7	2·2
48	F	20	–	8	0·8	1·7
49	F	31	–	8	0·9	1·8
50	M	24	–	5	0·8	2·3

CMV, closed mitral commissurotomy; Echo score, cross sectional echocardiographic score; MVA, mitral valve area, Pre, before balloon dilatation; Post, after balloon dilatation.

procedure. All were taking a β blocker at the time of the pre-dilatation test. The drug was stopped after the procedure so the patients were not taking β blockers for the post-dilatation treadmill test.

TECHNIQUE

All patients were given a β blocker for at least 48 hours as premedication before the procedure. Left and right heart catheterisation was performed from the left groin with measurement of cardiac output by thermodilution and left ventriculography immediately before dilatation. Transseptal puncture was performed via the right groin with a standard Brockenbrough needle and 8F Mullins sheath (USCI). A 7F balloon tipped flotation catheter with the balloon inflated was then introduced into the left atrium and then the left ventricle. Through this catheter a 0·038 inch extra-stiff guidewire (Cook) with a 2–3 cm handmade gentle curve at its tip was positioned in the left ventricular apex. The septum was dilated with a 10 mm balloon dilating catheter (Meditech). The mitral valve was dilated with either the bifoil (2 × 19 mm) or trefoil (3 × 15 mm) catheter (Schneider-Medintag). The dilatation catheter was introduced into the right femoral vein through a 16·5 French introducer sheath in the first nine patients but not in the others. After haemodynamic measurements were obtained, we repeated the right heart oximetry series and left ventriculography in all patients. The measurement of cardiac output by thermodilution was repeated with the deflated balloon across the septum so as to minimise any error due to atrial shunting. The mitral valve area was calculated by the original Gorlin formula. Mitral regurgitation was graded according to the method described by Sellers *et al.*[11] Heparin was administered via a peripheral vein (100 units/kg) after the left atrium had been entered. The anticoagulant effect was reversed with protamine sulphate (25 mg) at the end of the procedure.

STATISTICAL ANALYSIS

We calculated the mean and standard deviation and standard error for all variables. Haemodynamic changes before and after dilatation of the mitral valve were analysed by the paired *t* test. Stepwise multiple linear regression analysis (BMDP statistical package) was performed to establish a relation between the percentage increase in valve area or the development of mitral regurgitation and (*a*) balloon size, (*b*) balloon surface area per square metre body surface area, (*c*) balloon surface area per square centimetre mitral annulus area, (*d*) age, (*e*) severity of mitral stenosis, (*f*) echocardiographic score, (*g*) presence of mitral regurgitation before dilatation, and (*h*) mean pulmonary artery pressure.

Results

HAEMODYNAMIC CHANGES

The mitral valve gradient decreased from 12 (6) to 4 (3) mm Hg ($p < 0{\cdot}001$) and the average left atrial pressure decreased from 22 (6) to 13 (5) mm Hg ($p < 0{\cdot}001$). There was a significant increase in mitral valve area from 0·7 (0·3) to 2·1 (0·8) ($p < 0{\cdot}001$) and increase in cardiac output from 3·2 (0·7) to 4·0 (0·8) l/min ($p < 0{\cdot}001$). There was a significant immediate change in the mean pulmonary artery pressure (34 (14) to 31 (13) mm Hg, $p = 0{\cdot}01$) but no significant change in pulmonary vascular resistance (365 (292) to 352 (265) dyn s cm^{-5}. There was, however, a significant decrease in the systemic vascular resistance from 2043 (539) to 1664 (426) dyn s cm^{-5} ($p < 0{\cdot}001$).

Stepwise linear regression analysis showed that mitral regurgitation (MR) was related to the presence of mitral regurgitation before dilatation ($p < 0{\cdot}01$) and the severity of mitral stenosis ($p < 0{\cdot}01$) (MR = 1·786–1·379 (mitral area pre-dilatation) + 0·932 (MR), $R^2 = 42\%$. Regression analysis also showed that the percentage increase in mitral valve area was related to the severity of mitral stenosis before the procedure ($p < 0{\cdot}01$) (percentage increase in valve area = 371·870–223·728 (mitral area), $R^2 = 20\%$.

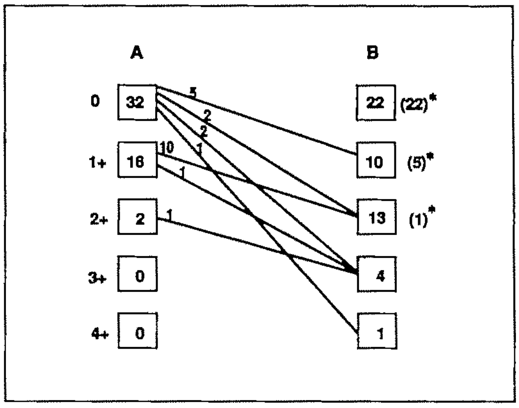

*Figure 1 Mitral regurgitation (A) before and (B) after dilatation. 0 = nil, 1 + = trivial, 2 + = mild, 3 + = moderate, 4 + = severe. *No change in grade of regurgitation.*

COMPLICATIONS

Mitral regurgitation was the most common complication (fig 1). In 22 (44%) of the 50 patients mitral regurgitation either developed for the first time or became worse. Most patients had trivial (5) or mild (12) regurgitation. In one patient severe regurgitation (grade 4) developed and he required emergency surgery. Mitral valve replacement was uneventful but he died in the postoperative period. Another patient with moderate mitral regurgitation (grade 3) underwent successful valve replacement for worsening cardiac failure four weeks after balloon dilatation. Of the remaining three patients with moderate regurgitation two were symptom free and one had grade II disablement at follow up 10 months later.

The development or increase in the grade of mitral regurgitation was predicted by the presence of regurgitation before dilatation and the severity of stenosis before the procedure. Cross sectional echocardiography immediately after the procedure showed a tear in the anterior mitral leaflet and chordal rupture in the patient with severe mitral regurgitation. Of the four patients with moderate regurgitation, chordal rupture was seen in two and a tear in the anterior cusp in one. None of the other patients with mitral regurgitation showed any abnormality on cross sectional echocardiography. The echocardiographic findings were confirmed in the two patients who had an operation.

A right heart oximetry series showed pulmonary to systemic flow ratios > 1·5 in four patients (1·6. 1·6, 1·7, and 1·9). There were transient ischaemic attacks in two patients, indicating embolic events. One had left hemiparesis and the other internuclear opthalmoplegia.

CLINICAL FOLLOW UP

In all but two patients symptoms improved. The New York Heart Association functional class (fig 2) improved to I in 45 patients, to II in three, and remained the same in two patients. It remained the same in the patient in whom severe mitral regurgitation (class IV) developed and in another who had moderate regurgitation after dilatation (class III). The average exercise time increased from 3·9 (2) to 7·2 (2) min ($p < 0·001$).

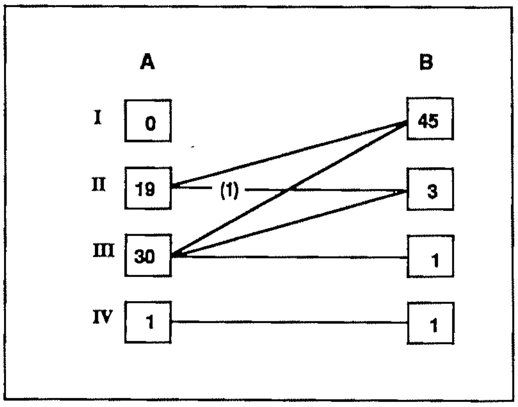

Figure 2 New York Heart Association functional class (A) before and (B) within one week of dilatation

Discussion

Since the pioneer work of Harken *et al*,[13] Bailey,[14] and Baker *et al*,[15] closed mitral commissurotomy has been the treatment of choice for rheumatic mitral stenosis. The technique has been perfected over the years and has become safe and effective. However, it has the drawback of being a surgical procedure. Over the past five years percutaneous balloon dilatation of the mitral valve has been tried as a treatment for stenotic mitral valves. The symptomatic and haemodynamic improvements after balloon dilatation by the single catheter technique (Inoue balloon catheter) and the double balloon technique have been well documented.[1–6] Experience with the bifoil or trefoil catheter has been limited.[8 9]

Commissural splitting has been shown to be the mechanism responsible for a successful result.[12–16] The size of the balloon has been shown to determine the area of the valve after dilatation.[10] Smaller balloons probably just stretch the valve apparatus and a balloon with a larger effective dilating area is required for adequate commissural splitting. Palacios *et al* recommended a balloon dilating area > 4·9 cm^2.[5] The average effective balloon dilating area in our series was 6·2 cm^2. Balloon dilatation with the bifoil catheter produced a larger mean (SD) valve area (2·2 (0·8) cm^2) than the trefoil catheter (1·8 (0·5) cm^2; but the difference was not statistically significant ($p = 0·2$). Our results are comparable to the calculated valve area achieved with the double balloon technique (table 2). The mean total duration of the procedure was 110 minutes (range 75–200) with a fluoroscopy time of 34 minutes (range 14–90). In the last 20 patients the mean fluoroscopy time was 19 minutes. A shorter fluoroscopy time is useful in pregnant patients with symptomatic mitral stenosis.

The severity of mitral stenosis was the only reliable predictor of outcome; the smaller the initial valve area, the larger was the percentage increase. Only five patients had valve area increase of < 100%. Studies of surgical commissurotomy and in vivo and in vitro balloon dilatation[10 17] showed that the structural features of the mitral valve determined the success of the procedure. Those with heavily calcified valves and subvalvar disease had smaller increases in valve area. Though the average increase in valve area was just over 200%, the range was wide (57–592%). We

Table 2 Results with double balloon technique

Authors	*Mitral valve area (cm²)*		*Percentage increase*
	Before	*After*	
Al Zaibag *et al*[3]	1·0 (0·3)	2·0 (0·8)	100
McKay C *et al*[12]	1·0 (0·3)	2·4 (0·8)	140
McKay C *et al*[4]	1·0 (0·3)	2·2 (0·7)	120
Kasab *et al*[7]	0·8 (0·1)	1·8 (0·3)	125
Chen *et al*[6]	0·8 (0·2)	1·9 (0·4)	138

failed to split the valve in one patient (fig 3) despite reasonable valve mobility and an echocardiographic score of 8. Partial splitting occurred in another five patients who had echocardiographic scores between 5 and 8. It is clear that some patients with good valve mobility have severe commissural fibrosis which results in a suboptimal result. We may also have underestimated the degree of subvalvar disease in this group of patients. In addition, some valves may merely stretch and recoil after balloon dilatation.

In the present series the pulmonary vascular resistance fell slightly but the fall was not statistically significant. The degree of relief of mitral obstruction does not necessarily correlate with the extent of the drop in the pulmonary vascular resistance after mitral valvotomy.[18] Our experience[19] and that of others[18] showed a progressive drop in the pulmonary vascular resistance with time. The mechanism by which the resistance continues to drop is not certain but changes in lung compliance and relief of vasoconstriction could explain these findings.

Mitral regurgitation remains a potentially life threatening complication of balloon dilatation of the mitral valve. In published reports its incidence varies from 0 to 50%. Severe regurgitation, however, is uncommon. Of the 22 patients (44%) in our study in whom regurgitation increased or developed, 12 had a prior mitral leak. Regurgitation after balloon dilatation was trivial or mild in most cases (17 patients). All except one of the patients with moderate (four cases) or severe regurgitation (one case) showed structural damage. Although the presence of mitral regurgitation before balloon dilatation predicted the development or worsening of regurgitation, most of these patients showed only a marginal increase in grade. Thus it seems that significant regurgitation will only occur when there is structural damage to the mitral valve. An oversized balloon catheter in the presence of significant stenosis (mean area = 0·7 cm²) may have played a role. In the patient with severe mitral regurgitation entanglement of the balloon with the chordae was believed to be the cause.

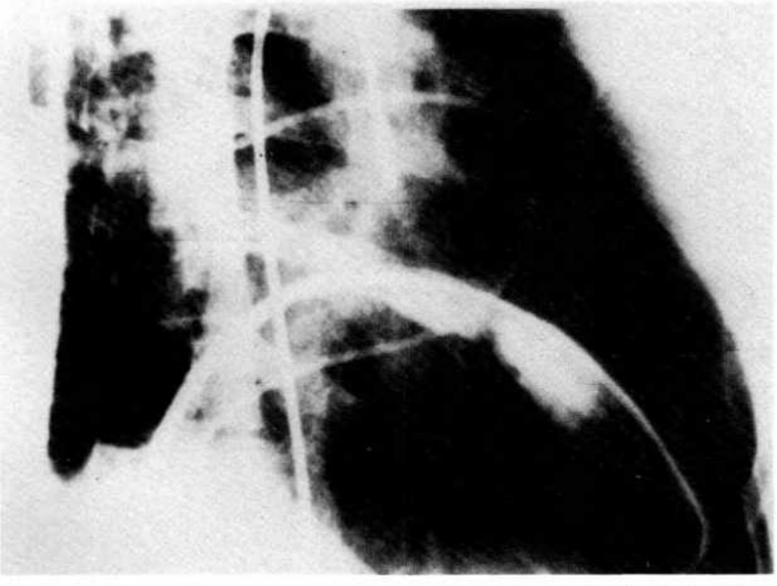

Figure 3 Trefoil catheter across mitral valve showing persistence of waist despite full balloon inflation.

The incidence of significant left to right shunting at the atrial level, as in other series,[4-6] was low. The long term effects of these shunts is unknown but there is some evidence that most atrial septal defects will close within 24 hours.[5]

The complications associated with the bifoil and trefoil catheters are similar to those experienced with the double balloon technique. Some say that it is easier and less damaging to introduce two small catheters into the femoral vein and across the valve. We did not have any technical difficulties introducing the bifoil and trefoil catheters into the femoral vein and across the valve and saw no bleeding or other complications at the venous puncture site. In fact the placement of two balloons may require more time and additional wire or catheter manipulation and we do not believe that the double balloon technique has any major advantages over the single catheter technique with the larger bifoil or trefoil catheters.

Balloon dilatation of the mitral valve has emerged as a definite alternative to surgical commissurotomy. The single catheter technique with the bifoil or trefoil catheter results in haemodynamic and clinical improvement that is comparable to that obtained with the double balloon technique. The average dilating area of the balloon (6·0–6·5 cm²) seems to be adequate in most cases. Additional studies need to be done to assess the safety and efficacy of percutaneous balloon dilatation with different techniques and catheters. We believe that the single catheter technique achieves acceptable valve areas, compares favourably with the double balloon technique, and may be more cost effective (because it uses fewer guidewires and catheters).

We thank Mrs Amelia Smyth for statistical guidance and the staff of the cardiac catheterisation and non-invasive laboratories for their technical assistance.

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Br Heart J 1990,64.347–8

LETTERS TO THE EDITOR

- *The British Heart Journal welcomes letters commenting on papers that it has published within the past six months.*
- *All letters must be typed with double spacing and signed by all authors.*
- *No letter should be more than 600 words.*
- *In general, no letter should contain more than six references (also typed with double spacing).*

Non-invasive determination of cardiac output by Doppler echocardiography and electrical bioimpedance

SIR,—Dr Northridge and colleagues (1990;63:93–7) have, inadvertently I am sure, incorrectly cited the proper name of the stroke volume equation currently implemented in NCCOM3. While it is true that the general form of the equation of Sramek *et al*,[1] quoted under patients and methods, describes impedance derived stroke volume in a general, qualitative fashion, it is the quantitative definition of volume of electrically participating tissue (VEPT) in the equation that requires clarification.

In the work cited by Northridge and associates, the VEPT defined by Sramek *et al*[1] is determined in practice uniquely as a function of body height alone. However, as correctly stated by Northridge *et al*, VEPT as currently used is a constant derived from both body height and weight. NCCOM3 computes stroke volume from the Sramek equation corrected for body habitus.[2 3] This modified equation is now generally cited as the Sramek-Bernstein equation,[4–7] which is the one, apparently, used in this study.

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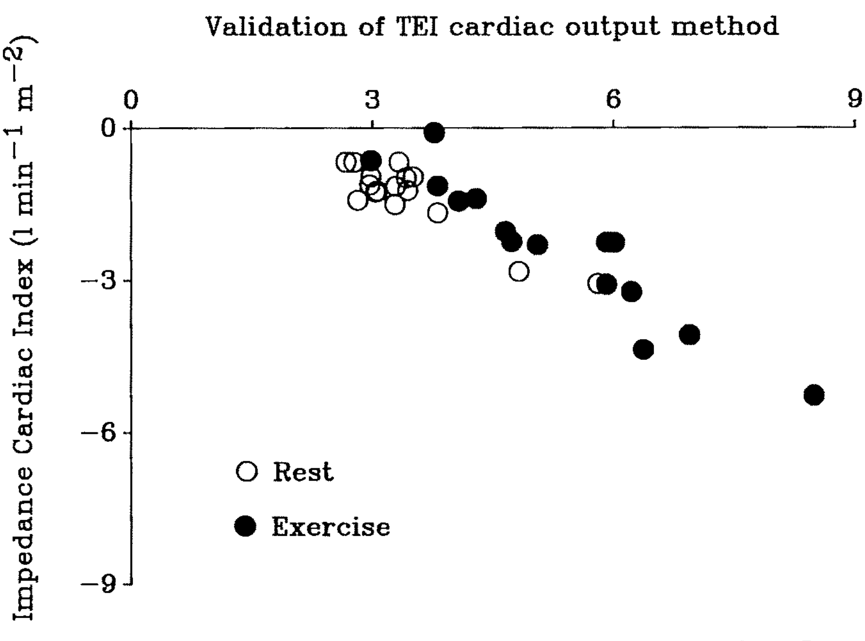
SIR,—We read with interest the validation of the transthoracic bioimpedance cardiac output device (BoMed NCCOM3) in acute myocardial infarction (1990;63·93–7). Northridge *et al* concluded that in most patients the transthoracic electrical bioimpedance technique was accurate and reproducible. The validity of this technique has been questioned[1]; we recently concluded that impedance cardiac output as implemented in the BoMed NCCOM3 was "not accurate compared with the thermodilution reference nor was it quantitative".[2]

There are many pitfalls in the assessment of cardiac output and in undertaking validation studies in humans[3] and assessment of devices likely to be applied in critical care should be rigorous rather than enthusiastic. Validation in vitro and in vivo should be attempted, the method should be accurate compared with the reference standard, and show similar reproducibility with ability to track physiological events and the effects of pharmacodynamic interventions.[4] A simple rest assessment may have serious limitations and result in misleading conclusions

Several crucial points in the Northridge paper may have contributed to the outcome. It is unclear whether investigators were blind to each other—this should be mandatory to avoid unconscious bias. Ten averaged estimates of impedance cardiac output were compared with three averaged thermodilution estimates: this is not reasonable. After the establishment of control haemodynamic stability, measurements should be paired, simultaneous, and consecutive; discarding of data ("outliers") and averaging generates spurious accuracy. The reference thermodilution system is at best under conditions of physiological stability.[3] Perusal of the data on control cardiac output (3·95 l/min) indicates that this lies outside the 95% confidence limits for acute heart failure (mean 4 31 (95% confidence interval +0·16) based on 32 studies of acute heart failure[5]); this suggests haemodynamic compromise, with subjects unlikely to be haemodynamically stable. Validation studies should cover as wide a range of comparison points to ensure the method has no systematic bias; clearly this was not achieved because of the patient population selected. In three of the patients there were considerable discrepancies between the methods—were these with higher cardiac outputs?

Our assessment of the BoMed impedance device in 16 patients with stable coronary disease was as follows.[2] Ten consecutive cardiac output measurements were compared with 10 impedance estimations over a 15 minute period. Subjects were studied fasting without premedication after a period of submaximal exercise to minimise haemodynamic variability. Observers were blind to each other; the thermodilution method had previously been validated in vitro and in vivo with accuracy and reproducibility determined.[3] Data were not averaged and all data were included to obviate observer bias. The data (figure) clearly suggested large discrepancies between the impedance estimate of cardiac output and the thermodilution reference (average difference 1·33 l min^{-1} m^{-2}; 95% limits of agreement 0·13 to 2 79 l min^{-1} m^{-2}). During 4 minutes supine bicycle exercise, with techniques to minimise chest movement, these differences increased (average difference 2·36 l min^{-1} m^{-2}; 95% limits of agreement −0·56 to 5·28 l min^{-1} m^{-2}). We concluded that the BoMed impedance method as currently implemented in the NCCOM3 device produced uniformly low values compared with thermodilution estimates, suggesting that the incorporated algorithms were not appropriate to the ischaemic population. Our observations suggested that the method at present is unacceptable for scientific or clinical applications.

Devices which rely on empirically determined formulas (impedance changes in transthoracic impedance have been correlated with cardiac stroke output in volunteers) depend absolutely on the reliability of these relations; it may be oversimplistic to expect similar volume conduc-



Validation of transthoracic bioimpedance (TEI) method.

tance characteristics in normal volunteers and patients with coronary disease (many with concomitant respiratory disease). Though the bioimpedance technique has undoubted potential for non-invasive cardiac output determination in humans, the NCCOM3 technique is not a satisfactory implementation of this method.

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These letters were shown to the authors, who reply as follows:

SIR,—We are grateful for the opportunity to reply to the points raised in these two letters.

We agree entirely with Dr Shoemaker's comments. The bioimpedance stroke volume equation used in the BoMed NCCOM3 was first described by Dr Sramek. The contribution of Dr Bernstein, which we would not wish to underestimate, was an improved method for calculating VEPT (one variable in the Sramek equation) rather than a modification of the equation itself. As stated in our paper, VEPT was determined from both body height and weight—the Bernstein method.

We take issue with many of the points raised by Dr Silke. The thermodilution results were taken simultaneously with electrical bioimpedance by two blinded observers. As we stated, the bioimpedance estimate was taken as an average of 120 heart beats, not 10. This was compared with three averaged thermodilution estimates because these require a similar length of time. Each thermodilution estimate is in itself an average over a number of cardiac beats. We disagree with Dr Silke's assertion that averaging generates spurious accuracy. In fact we deliberately made only one estimate of cardiac output with each method per patient to avoid the spurious correlations that can be generated when multiple measurements are made in the same patient.

We do not follow Dr Silke's reasoning regarding the haemodynamic status of our patients. They were not chosen for their haemodynamic stability—unlike the patients included in the drug studies cited. Since we made the thermodilution and bioimpedance measurements simultaneously, any haemodynamic instability would not bias our results.

Dr Silke suggests that we did not study a wide enough range of cardiac outputs In fact the thermodilution results ranged from 2 l/min to over 6 l/min which covers most values commonly encountered in clinical practice. He also suggests that the three patients in whom there was considerable disagreement between electrical bioimpedance and thermodilution might have been those with the highest cardiac outputs. Inspection of figure 3 of our original paper clearly shows that this was not the case. There was no relation between the size of the errors and the mean of the two estimates of cardiac output.

There are several possible reasons to explain the poorer results obtained by Dr Silke with electrical bioimpedance. However, it is difficult to compare our methods because his study has not been published in full. The most obvious difference between the studies is that our measurements were not made during exercise. A previous report concluded that the BoMed NCCOM3 was inaccurate during exercise.[1] Another problem with Dr Silke's study is that electrical bioimpedance is compared with thermodilution—a technique that may be unreliable during exercise because of the development of tricuspid incompetence.[2] Therefore the lack of agreement between bioimpedance and thermodilution during exercise should not discourage physicians from using this device in patients at rest, especially to monitor changes in cardiac output.

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Br Heart J 1990;64:349

VIEWS FROM THE PAST *Ronald Thomson Grant 1892–1989*

After leaving the Army in 1919 at the age of 27, Grant took a house job at the Ruchill Fever Hospital, Glasgow and learnt to use a Mackenzie polygraph which happened to be there. This aroused his interest in cardiology and Dr (later Sir) John McNee obtained a post for him in Dr (later Sir) Thomas Lewis's Medical Research Council funded cardiographic department at University College Hospital, London, where he was to stay for 14 years. Lewis was working intensively on atrial flutter and fibrillation and had just proposed his famous hypothesis of "circus movement" to explain their mechanism. Grant's first paper with C C Iliescu was a comparison of the effects of four cinchona alkaloids on the atrial and ventricular rates in atrial fibrillation; quinidine was the most effective.

Then in 1923 Grant and Lewis wrote a 78 page paper entitled "Observations relating to subacute infective endocarditis." This included a good histological study showing that the position of the valve annulus in the aortic wall would reliably distinguish a congenital from an acquired bicuspid aortic valve. Grant cut and stained all the sections himself. His interest in cardiac pathology continued in three papers on congenital heart disease based on cases of partial heart block in single ventricle, congenital pericardial deficiency, and anomalous coronary arteries. He also wrote on the comparative anatomy of the coronary arteries. By 1923 Lewis had completed his electrocardiographic research and had started to work on the vascular reactions of the skin to injury, designating the red line flare and weal produced by a heavy stroke to the skin as the "triple response". Grant and Lewis then showed that many different forms of injury gave this response and by a long series of simple but intellectually brilliant experiments they showed that injury releases a histamine like body from the tissue cells. They called it "H substance".

By 1932 Grant had completed a remarkable 10 year follow up of 1000 former soldiers with organic heart disease. It had been the first task given to him on joining the department and he wrote it up in a 58 page paper with 147 pages of tables. Many features were analysed and he showed that the two best prognostic indices were exercise tolerance and cardiac enlargement. This large statistical study must have been one of the first of its kind. It included a pioneer controlled trial of treatment in which 175 patients with syphilitic heart disease were given either arsenic, mercury, and iodides; or iodides only; or placebo. Death rates at 10 years were 48%, 64%, and 67% respectively.

Lewis's campaign to promote clinical science was now in full swing. He was keen to establish departments of clinical research elsewhere and persuaded the Medical Research Council to set up one at Guy's Hospital with Grant as director. (Lewis's salary was now being met by the Rockefeller Foundation which released Medical Research Council funds for the new post.) Their association continued in the Medical Research Society. Later in life Grant told me that he had been happy working in the department with no wish to leave despite the fact that "the discomfort was that you were all the time aware of your own deficiencies when you were with Tom. He found it easy to see and put things clearly and if you did not—well you were just a fool and you were pretty well told so. But if you fought back and showed reason he would take it easily. There was a zeal for the truth and you felt this man is really serious and you put up with a hell of a lot from a man of that quality. Sometimes I felt I must get out of this I can't stand it any more but then again you felt I'll beat him—that was the feeling he aroused in you."

In his last years at University College Hospital Grant's interests had turned to the peripheral circulation and his first paper from Guy's Hospital with H E Holling was on the vascular response of the limb to body warming with evidence for sympathetic vasodilator nerves. Subsequent papers were on polyarteritis nodosa and pulmonary fat embolism.

The heavy bombing of the London docks in 1940 led to many severely injured patients being admitted to Guy's Hospital and at the suggestion of Dr E B Reeve, Grant set out to study shock—not an easy task. For a while the famous philosopher L Wittgenstein became his technician having first come to Guy's Hospital as a porter to help the war effort. Remarkably, at the age of 52 Grant formed the Royal Army Medical Corps Traumatic Shock Research Unit. He had the rank of Lieutenant-Colonel and pursued his studies for several months during the Italian campaign sometimes working within 10 miles of the battle front.

He set high standards and could be a demanding person to work with but he was essentially a kind, friendly, generous, and approachable man whose modesty added to the respect in which he was held.

ARTHUR HOLLMAN

BRITISH CARDIAC SOCIETY NEWSLETTER

You have voted to return to Wembley for the spring meetings in 1993 and 1995. The majority was a narrow one: 144 in favour of Wembley and 135 against. This may surprise many who were so enthusiastic about Torquay, and those who worked in London who found it was helpful to be away from the shop. Perhaps many who voted for Wembley had not been to Torquay or do not work in London . . .? The President wondered about giving two votes to Officers or making an adjustment for the many abstentions; but the first option would not have worked, and the second was overruled by his democratically minded colleagues. The Officers' discussions after the Torquay meeting did not bring to light any major problems relating to the organisation. The sessions went smoothly, but we did receive comments on some of the slides from Mr Tony Oxley who is our new consultant on audiovisual aids. The mounts should be of good quality, and with glass. Remember that the projector lamps are very powerful, and therefore very hot. This may not cause a problem during short presentations, but in plenary sessions poor quality slide mounts are liable to cause problems.

The society received 19 applications for travel scholarships for the Stockholm meeting. As usual, priority was given to those presenting papers at the meeting who could not obtain appropriate support from other sources. We received 19 applications, of which 17 were deemed very suitable and given funding. Members are reminded of this facility For the next meeting we plan to make 25 scholarships available and we hope to receive applications from all those qualified to receive them.

What do members think about the tradition that only surnames should be used during official business of the society? The astute among you – presumably all – may have noticed that the practice has not been observed consistently in the newsletter The sky has not yet fallen, and indeed not a single letter of protest has been received. Is the tradition outmoded? Few would favour the artificial bonhomie of first names used as a routine, but should we not move into line with usual social conventions whereby both first names and surnames can each be used as is appropriate. We look anxiously to the sky . .

The membership of the Data Management Committee was mentioned in the September newsletter: Parker (chairman), Campbell, Hubner, Macfarlane, Nathan, Poloniecki, Rickards, Chamberlain, K Taylor, and a paediatric cardiologist. Michael Tynan has now agreed to fill the paediatric slot, and the committee has been enlarged by the addition of another District General Hospital cardiologist – Tony Mourant. This is an important committee for many reasons, but not least because of the implications for audit. It is setting about the task of developing an agreed data dictionary for all the major areas of cardiology and cardiac surgery in regional centres and district general hospitals. This must work in conjunction with the clinical information services that are being introduced into the National Health Service.

You will soon be seeing the results of the 1990 staffing survey that was completed in August. The growth in consultant numbers remains at about 5% a year and this must be maintained for the next decade if we are to match by then the target of 150 new posts that we calculate we need now for adequate provision of the service. This number is made up of 60 new posts for the centres to cope with the present shortfall plus the emerging needs of angioplasty, 40 new posts for districts that at present have no cardiologist, and 50 posts for the larger districts that have one post but by our existing guidelines need two. By the end of the decade the goal posts will have moved so it may be a very long time before we catch up with our true requirements. We have to watch carefully the number of training posts to ensure that we will be able to meet future growth, as well as the need for replacements Retirements do tend to be cyclical and our predictions based on our surveys are therefore of critical importance. They have proved reliable over the past 12 years and they will continue to give us the information we need. Our hope is that the system can be flexible enough to respond to future requirements. We have long known that a bulge in retirements starts in 1997 and continues for several years thereafter. Our training programmes extend over six or seven years so we must be looking ahead now if we are not to have a shortfall. At present we probably have too many within the registrar grade who aspire to a career in cardiology. This requires an adjustment which will be made by the Joint Planning Advisory Committee under the guidance – we trust – of the Royal College of Physicians in conjunction with the society. But we are likely to need some increase in senior training posts, and we must resist unrealistic cuts at registrar level. The reductions in the number of registrars is intended to be a 10 year programme and there are grave risks in making cuts that are rapid and Draconian.

Publication of the current staffing survey is being held up because we wish to include with it the results of the 1989 facilities survey. This was not completed last year because many districts (including several major centres) did not return their questionnaires despite several reminders by post and telephone. Please remember that data provide strength to our negotiating position. The new arrangements, whereby our surveys are conducted by the Trafford Centre which is within the University of Sussex and under the direction of Richard Vincent, enable us to be more persistent. At the end of the day the minority of recalcitrant colleagues (we sympathise with their problems though we won't admit it) will realise there is no reasonable escape and rapid response may be easiest in the end. That is the view we are anxious to promote, especially as surveys are now to be annual rather than biennial events. Meanwhile only a few districts are holding out and the forces arrayed against them are gaining strength. When you read this the battle will be won.

DOUGLAS CHAMBERLAIN
President, British Cardiac Society
PAUL OLDERSHAW
Secretary, British Cardiac Society,
4 St Andrew's Place,
London NW1 4LB

NOTICES

British Cardiac Society
The Annual Meeting will take place at the Scottish Exhibition Centre, Glasgow on 30 April to 3 May 1991. The closing date for receipt of abstracts will be 10 December 1990.

Cardiology and cardiac surgery
An international workshop on Updates in Cardiology and Cardiac Surgery, jointly organised by the Heart Institute, St Vincent's Hospital and Medical Center, Portland, Oregon, and the Institute of Cardio-Vascular Diseases, Madras will be held in Madras on 11 to 13 January 1991. Information from Institute of Cardio-Vascular Diseases, 180 NSK Salai, Madras – 600 026, India

Cardiac pacing and electrophysiology
The IXth World Symposium on Cardiac Pacing and Electrophysiology will be held in Washington, DC on 28 to 31 May 1991. For information write to the North American Society of Pacing and Electrophysiology, 377 Elliott Street, Newton Upper Falls, MA 02164, USA.

Computers in cardiology
The Eighteenth International Conference on Computers in Cardiology will be held in Venice on 23 to 26 September 1991. Inquiries to Computers in Cardiology, c/o LADSEB-CNR, Corso Stati Uniti 4, 35020 Padova, Italy Telephone: +39-49-8295702. Fax. +39-49-8295649.

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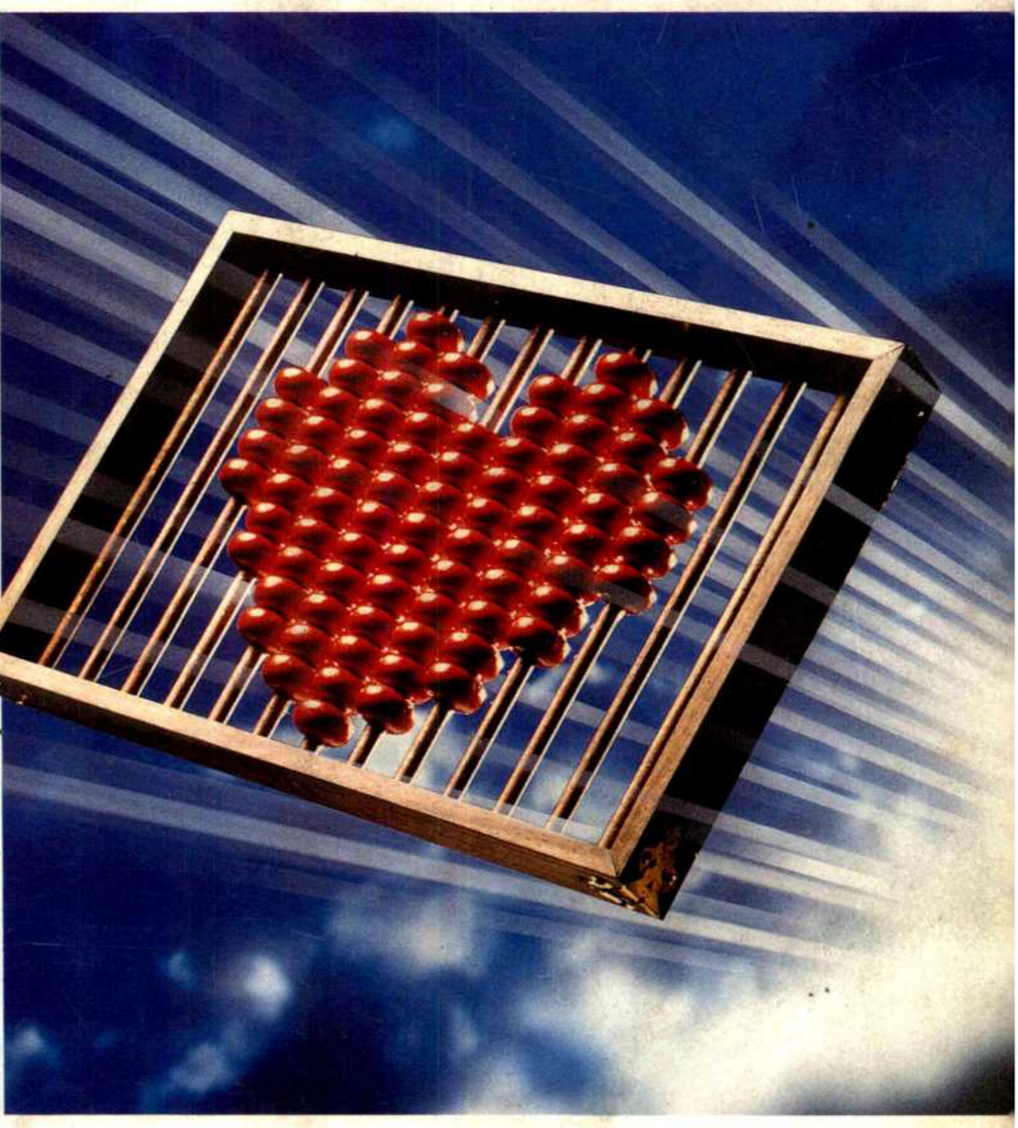

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BRITISH
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REVIEW

Restenosis after angioplasty

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Coronary angioplasty is now an accepted form of treatment for patients with ischaemic heart disease. In the United States 100 000 procedures were performed in 1988; and in 1990 the procedure will reach parity with coronary surgery. In the United Kingdom just over 5000 procedures were performed in 1988.[1] It is clear that angioplasty is here to stay and that the indications, particularly in the United Kingdom, will expand. More operators will undertake multivessel, multilesion dilatations, though the results of various comparative trials such as the Coronary Artery Bypass Revascularisation Investigation (CABRI), Randomised Intervention Treatment of Angina (RITA), Bypass Angioplasty Revascularisation Investigation (BARI), and Emory Angioplasty Surgery Trial (EAST) may influence patient selection for percutaneous transluminal coronary angioplasty. The major limitation of this procedure is the high incidence of restenosis. Despite increased understanding of the pathophysiology of restenosis over the past ten years we are still unable to influence significantly the rate of this complication. The incidence of restenosis varies between 17% and 40%.[2–6] The variation may be the consequence of whether there has been complete angiographic follow up as well as the way that restenosis is defined.

Pathophysiology

Balloon angioplasty causes longitudinal and circumferential splits in the vessel wall with disruption of the endothelium, intima, and media.[7 8] Healing involves endothelial regrowth and stabilisation of the intimal and medial injury. In general, superficial endothelial injury leads to local platelet and leucocyte adhesion, but most of the platelets do not undergo a release reaction. In these circumstances re-endothelialisation is rapid and there is no subintimal proliferative response. The response to deep endothelial injury, which by definition occurs in successful angioplasty, is more complex, however. Platelet activation may be initiated by contact with deep intimal or medial collagen and contact with microfibrils and basement membrane contained within the vessel wall. Coagulation factors may be released from damaged cells, and intramural thrombus formation is probably common. The rate and adequacy of human endothelial regrowth have not been studied, but may be slow and incomplete. Part of the repair process involves the proliferation and migration of medial smooth muscle cells.

Restenosis after angioplasty is most commonly due to an excessive local proliferation of these smooth muscle cells—fibromuscular intimal hyperplasia. This has been shown both at necropsy[9] and more recently in vivo by means of atherectomy devices.[10 11] Because activated platelets release platelet derived growth factor, which has been shown to cause migration and to influence proliferation of smooth muscle cells in vitro, it is tempting to link this proliferation with platelet activation and release at the time of the original injury, or with the continuing effects of platelet activation in the presence of a leaky endothelium. Any such theory has to take into account, firstly the relatively slow time course of restenosis and, secondly the failure of platelet inhibitory treatments to influence it in any way. There have been several clinical trials of aspirin, fish oils, and other substances known to affect platelet function. Trials of aspirin in the prevention of restenosis have been unsuccessful, irrespective of the dosage used.[12–15] In one animal model of intimal hyperplasia aspirin actually enhanced proliferation, possibly by blocking prostacyclin production.[16]

Aspirin may be ineffective because it inhibits the wrong pathway in platelets, because the process of proliferation, once started, is self perpetuating, or less likely because platelet activation really has nothing to do with restenosis. The cyclo-oxygenase pathway that is blocked by aspirin is not required, for example, for the adhesion and activation of platelets by fibrillar collagen, thrombin, or platelet activating factor, all of which are likely to be exposed after angioplasty damage. Indeed it has been shown that platelets can adhere and be activated by collagen in the presence of aspirin. Much more potent platelet anti-aggregants are now available, including monoclonal antibodies to the glycoprotein IIb/IIIa integrin complex and von Willebrand factor, and snake venom peptides containing the specific platelet adhesion sequence. The problem is that they have greater effects than aspirin on haemostasis and their long term use is unlikely to be practicable. Additionally, von Willebrand factor and the glycoprotein involved in it causing platelet adherence (glycoprotein Ib) may be important only at high shear stress, a state unlikely to be present after successful angioplasty.

An initial proliferative response, set off by injury, with or without a contribution from platelets, might become self perpetuating. In vitro work suggests that only certain smooth muscle cell types proliferate and migrate[17] and also that under certain circumstances smooth muscle cells (modified mesenchymal type) may themselves secrete active growth factors, thus producing a "positive feedback" effect.[18] This has not been shown, however, for all types of proliferating smooth muscle cells. Alternatively, the initial proliferative stimulus may activate clones of smooth muscle with a greater proliferative capacity and less sensitivity to the usual controls (as shown by the Benditts' work on clonality in atheromatous plaques[19]). The ability to retrieve proliferating smooth muscle from the vessel during coronary atherectomy will enable both hypotheses to be tested. If it can be shown that the initial trigger is required for a short time only and that the smooth muscle cell response becomes self perpetuating or independent thereafter then a case could be made for short term, high intensity treatment to prevent an excessive platelet/thrombotic response,[20] followed by longer term treatment aimed more directly at controlling smooth muscle proliferation. A recently completed study undertaken at the London Chest Hospital showed that prostacyclin given as a 36 h intravenous infusion in doses that can be tolerated did not prevent restenosis.[21]

In vitro studies on smooth muscle proliferation emphasised the importance both of extracellular matrix and of families of growth factors whose peptide sequences have been determined but whose biological significance often remains unclear. One family of growth factors has a strong affinity for heparin; and the antiproliferative effect of heparin in some animal systems may be due to this rather than any effect on coagulation.[22 23] Cells that are moving into a proliferative phase often express the products of a series of genes called proto-oncogenes. A well known smooth muscle proto-oncoene called *mas* has recently been shown to control the expression of a receptor for angiotensin II. This may, or may not, have something to do with the empirical observation that angiotensin converting enzyme inhibitors can suppress vascular smooth muscle proliferation, and proto-oncogenes are currently being assessed for their ability to influence restenosis. Familiar drugs sometimes work in unfamiliar ways, and we are shortly likely to have more drugs available that have been specifically targeted against smooth muscle proliferation. We have been through the phase of attempting to do something about the platelets and have so far failed. This does not necessarily mean that blood factors are not involved or important—but we do not yet have readily available agents that can fundamentally modify the blood vessel wall interaction and retain an acceptable margin of therapeutic safety. Two major assets in the assessment of new drugs and other anti-restenosis strategies would be good animal models for restenosis and a much clearer and more logical approach to the measurement of human restenosis.

Definitions of restenosis

The patient and the referring physician, are primarily interested in the relief of symptoms and preventing their recurrence. Symptoms are too variable a phenomenon to allow scientific study of quantitation of restenosis or evaluation of measures to prevent it. In clinical trials there is no substitute for follow up angiography of *all* patients, something that has been lacking in many large follow up studies, particularly in the United States. There are several definitions of restenosis but they essentially fall into two groups: those based on relative measurements and those based on absolute measurements. Examples of relative measurements include "presence of a 50% diameter stenosis on follow up in a patient with less than a 50% stenosis immediately post angioplasty" and "a 30% increase in % diameter stenosis from the immediate post angioplasty estimate". Holmes and colleagues compared four different "relative measurement" definitions of restenosis and found that the most sensitive was "loss of 50% of the gain in diameter at PTCA".[3] The major problem with relative measurements is that they assume that the diameter of a reference segment of the coronary tree will remain constant, and we now know that this assumption is invalid.

Serruys and his colleagues measured both stenosis and reference segment diameters immediately after angioplasty and at follow up (using catheter tip size as a further internal reference marker) and found a significant reduction in reference segment diameter in patients with restenosis.[24] There is a straightforward biological explanation for this: we now know that the arterial diameter is actively modulated by endothelial shear stress, probably working through endothelium derived relaxing factor (nitric oxide); a stenosis will reduce runoff and diminish flow velocity and hence shear stress in the segment proximal to it, with consequent involution of the vessel. If we use another vessel rather than a proximal segment as the reference point, the converse will apply, with increased collateral circulation perhaps increasing the reference segment diameter. To take an extreme example, suppose we start with a 1 mm diameter stenosis in a 3 mm vessel and dilate it to 2 mm. At follow up the treated segment has reverted to a diameter of 1 mm, but the reference segment has involuted to a diameter of 1·5 mm. In relative terms there is no restenosis, but obviously the procedure was a biological failure. The Rotterdam group have suggested that the criterion for restenosis should be a decrease in stenosis diameter which is equal to or more than twice the standard deviation for the variability in making repeated measurements of vessel diameter. For the technique they use this is 0·72 mm. The use of twice the standard deviation is a long established scientific convention; it is perhaps unfortunate that the figure of 0·72 mm has sometimes been quoted out of context and therefore seems arbitrary whereas it is merely a statistical measurement, derived from the Rotterdam group's *own* data, that takes account of the change that could be due to chance when a lesion is observed on two occasions. Application of such a figure to individual lesions measured by different techniques or in different patient groups may be inappropriate. In the study recently completed at the London Chest Hospital the standard deviation of the measurement of video densitometry was 0·315 mm (0·63 mm = 2 SD).[21]

The other problem with measuring absolute change and its standard deviation is that it does not take account of what would have happened if there had been no angioplasty—this information can only be obtained by some reference to the native, non-angioplastied coronary circulation. It may be true that overall the trend is for the reference "normal" diameter lumen to fall with time, however, the individual will vary and indeed the diameter of a non-angioplastied vessel could actually increase in some individuals. Nobuyoski *et al* have combined the apparent benefits of using absolute values with the sensitivity of the "loss of 50% of the gain" definition.[25] This is probably a good compromise, with restenosis being defined as "loss of 50% of absolute gain in mm".

As newer techniques appear the precision of measurement will improve and the criteria of restenosis will seem to get stricter. This does not matter if all we are interested in is the scientific comparison of two groups of patients in a controlled trial. In this case, we should avoid arbitrary definitions of restenosis and use absolute changes in stenosis diameter as continuous variables (any apparent advantage in using stenosis area rather than mean diameter is probably illusory). Whichever definition is used for restenosis it needs to be clearly stated and justified in any published data.

Conclusion

It is clear that restenosis is still a major problem after percutaneous transluminal coronary angioplasty. The data of Serruys and Nobuyoski indicate that the restenosis rate peaks within the first six months and is at least 25%[22] and may be 49%.[23] Until there are drugs that significantly inhibit adhesion of platelets to damaged vessel walls or until there is some way of making the damaged vessel wall unattractive to platelets, it may be more useful to turn our attention to preventing the consequence of the release of growth factors by platelets and white cells—namely smooth muscle cell proliferation. Drugs are currently being evaluated that may limit the response of the smooth muscle cells. Only when the restenosis rate is reduced will percutaneous transluminal coronary angioplasty have fulfilled its true potential. To allow this we need clear definitions of restenosis applied to well constructed properly controlled clinical trials with high angiographic follow up.

1 Hubner PJB. Cardiac interventional procedures in the United Kingdom during 1988 *Br Heart J* 1990,64:36–7
2 Kaltenbach M, Kober G, Scherer D, Vallbracht C. Recurrence rate after successful coronary angioplasty *Eur Heart J* 1985,6 276–81.
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Christmas editorial

Up tempo, down tempo

There is a poorly researched consensus that 2/4 and 4/4 rhythms originate from imitations of the human heart-beat and some evidence that changes in the tempo of music induce changes in the heart rate and mood of the listener.[1] Recordings of instrumental music reduced complications in patients admitted to a coronary care unit with presumed myocardial infarction.[2] Another study, however, showed that those left in peace fared just as well.[3] In a neonatal intensive care unit the Moonlight Sonata played to premature infants (gestational age 33–35 weeks) significantly reduced heart rate, blood pressure, and respiratory rate: a recording of the Sabre Dance did not.[4]

A study reported in this issue (p 388) shows that the heart rates of orchestral musicians rose significantly during rehearsals and performance. The effect of playing music on heart rate was greater for the music of Rachmaninov and Tchaikovsky than for Richard Strauss and Mozart. Some individuals achieved heart rates that they would probably have had difficulty in sustaining had these rates been induced by exercise.

Surveys of performing instrumental musicians show that about half of them have medical problems related to playing, some of which threaten or terminate their careers.[5] Recently, there have been indications that these problems have gained wider recognition and have been treated more sympathetically.[6] The main problems are psychological stress, including stage fright, and muscle overuse syndromes.

A study of orchestral players in London commissioned by the British Performing Arts Medicine Trust showed that among 222 musicians 72% experienced nervousness during a performance that interfered with their playing and a fifth of these reported that this happened frequently.[7] In that survey 21% took β blockers, tranquillisers, or alcohol to control nervousness before a performance, and 28% took one or other of these agents before an audition. Musicians from provincial British orchestras gave more concerts and had fewer rehearsals than those in continental Europe. Not surprisingly, the British musicians had more performance-related anxiety than their continental counterparts.[7] The risks and benefits of β receptor blocking drugs and tranquillisers for musicians should be carefully assessed in each individual.[8]

In the United States, a survey organised by the International Conference of Symphony and Opera Musicians showed that 39% of 2212 players from 47 orchestras who responded had psychological problems including acute anxiety in 13% and cardiovascular problems in 18%.[5] These cardiovascular problems included hypertension (10%) and "heart conditions" (4%) and their occurrence was positively correlated with the musician's perception of the amount of stress experienced.[9] Some 40% of the orchestral musicians surveyed had tried prescribed medication for the treatment of stage fright and most (92%) had found it effective. The drugs most used were β receptor blocking agents and 27% of the musicians had used propranolol or some other β receptor blocker. Women (31%) were more likely than men (26%) to use these drugs and they were more commonly taken by those under 35 (30%) than by those over 45 (20%). Not all use of β blocking drugs among orchestral musicians was for treatment of stage fright: 19% of users had them prescribed daily for conditions affecting the heart, for headache, or for some other indication. Another group (11%) had been prescribed β receptor blocking drugs but took them occasionally, presumably for stage fright. In this American survey, however, most of those using β receptor blocking drugs did so without a doctor's prescription. Those who had been prescribed β blockers, both inside and outside the orchestra, were the major suppliers of β blockers to musicians.

Does this occupational stress matter? In terms of the happiness of individual musicians and the difficulty that they have in maintaining cardiovascular fitness in a sedentary occupation, it might be surmised that they mostly have short, unhappy careers. However, a fascinating study of retired musicians all aged over 80 from one of America's great symphony orchestras challenged this view.[10] Their careers, which began in the 1920s and 1930s, were long and some retired only when they were well over 70. Players of string instruments had longer careers than players of brass and woodwind instruments. Although these retired musicians continued to love music and to listen to it after retirement, few continued to play seriously.

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ORIGINAL ARTICLES

A systemic non-lytic state and local thrombolytic failure of anistreplase (anisoylated plasminogen streptokinase activator complex, APSAC) in acute myocardial infarction

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Abstract
The relation between coronary thrombolysis and coagulation variables after administration of anistreplase (anisoylated plasminogen streptokinase activator complex, APSAC) was studied in patients with an acute myocardial infarction. Fifty eight consecutive patients with acute myocardial infarction were given 30 U of anistreplase intravenously within 4 hours of the onset of symptoms. A fall in the plasma concentration fibrinogen to <1·0 g/l 90 minutes after administration of anistreplase was considered to reflect a systemic lytic state. Coronary angiography was performed 48 hours after thrombolytic treatment. The overall patency rate was 74% (43/58). Patency rates were significantly different in patients with a systemic lytic (83% (43/52)) and a systemic non-lytic state (0% (0/6)). The absence of a systemic lytic state after anistreplase administration seemed to be highly predictive of the failure of coronary thrombolysis. Coagulation studies showed evidence of inhibition of anistreplase induced fibrinolytic activity which may explain the failure of thrombolytic treatment in patients with evidence of a systemic non-lytic state.

Thrombolytic drugs reduced mortality in patients with acute myocardial infarction treated within 6, 12, or even 24 hours of the onset of symptoms.[1–3] When treatment was started within the first 4–6 hours after the onset of chest pain, reperfusion was shown in most of the infarct related coronary arteries. However, in up to 30–40% of the patients no reperfusion could be achieved.[4] Failure of thrombolytic treatment has been reported irrespective of the drug used.[4] The configuration of coronary obstruction may be an important determinant of the success of treatment,[5] but inhibition of drug activity has never been ruled out.

In general, streptokinase and anistreplase (anisoylated plasminogen streptokinase activator complex, APSAC) caused comparable changes in haematological variables such as fibrinogen, plasminogen, and α_2 antiplasmin during the first 24 hours after they were given.[6] These changes were ascribed to systemic effects. Some patients, however, showed no substantial decrease in plasma fibrinogen after anistreplase or streptokinase administration.[7] This suggests resistance to these drugs. It has been suggested that a systemic lytic state, defined as a low plasma concentration of fibrinogen after thrombolytic treatment, is a prerequisite for local thrombolytic efficacy.[8]

To investigate the possibility of drug resistance as an explanation for failure of thrombolytic treatment, we performed a retrospective study to assess the relation between the systemic fibrinolytic effects and the local efficacy of anistreplase in patients with acute myocardial infarction.

Patients and methods

PATIENTS

We studied 58 consecutive patients (47 men, 11 women), mean age 57 years (range 34–71), who presented within 4 hours of the onset of chest pain. Selection criteria for thrombolytic treatment included the presence of characteristic symptoms of myocardial infarction and ST segment elevation of at least 0·1 mV in one or more of the standard leads or at least 0·2 mV in two or more of the precordial leads in a 12 lead electrocardiogram and the presence of symptoms unresponsive to sublingual glyceryl trinitrate. We excluded patients with contraindications for thrombolytic treatment and those who had been treated with streptokinase or anistreplase within the previous 6 months.

STUDY PROTOCOL

Patients were treated with 30 U of anistreplase (Eminase, SmithKline Beecham) administered intravenously in 4–5 minutes. Infusion with heparin (30 000 U in 24 hours) was started 4–6 hours after thrombolytic treatment and was continued until an adequate level of anticoagulation had been achieved with oral acenocoumarol, which was started after 48–72 hours. To assess patency of the infarct related artery, coronary angiography was performed

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48 hours (range 36–60) after the administration of anistreplase in all patients. In the first 30 consecutive patients patency was also assessed after 90 minutes (range 1 to 3 hours). Patency was documented according to the score used in the thrombolysis in myocardial infarction (TIMI) trial.[9] Scores of grade 0 or 1 indicated occlusion of the infarct related vessel and grades 2 and 3 patency.

COAGULATION ANALYSES

Coagulation and fibrinolytic variables were studied immediately before and 90 minutes and 48 hours after anistreplase administration. Venous blood samples were collected on ice in a 1/10 volume 3·05% trisodium citrate for measurements of fibrinogen, plasminogen, α_2 antiplasmin, reptilase time, and euglobulin clot lysis time. Assays were performed immediately or plasma was stored at −80°C for analysis later. Fibrinogen was measured according to the method of Clauss.[10] Plasminogen and α_2 antiplasmin assays were performed with a synthetic chromogenic substrate (Kabi) according to the method of Friberger *et al.*[11] Reptilase time was determined by the method of Soria *et al*[12] and euglobulin clot lysis times by the method of Buckell.[13] The assay for fibrinogen/fibrin degradation products was carried out on serum collected at the times mentioned above with a latex agglutination kit (Wellcome) according to the method of Pitcher.[14]

A systemic lytic state was defined as a decrease of the plasma concentration of fibrinogen to below 1·0 g/l, measured 1·5 hours after the administration of anistreplase.

STATISTICAL ANALYSIS

Plasma concentrations of fibrinogen, plasminogen, and α_2 antiplasmin were expressed as mean (SD). Statistical comparisons between patients showing a systemic lytic state and a systemic non-lytic state were performed by means of Student's *t* test for independent samples. Comparisons within the groups were made with the paired Student's *t* test.

Measurements of reptilase time, euglobulin clot lysis time, and fibrinogen/fibrin degradation products were expressed as median (range). Patient groups were compared by the Mann-Whitney U/Wilcoxon rank sum test. Differences within the groups were tested by the Wilcoxon matched paired signed ranks test. We used Fisher's exact test to compare the result of treatment in terms of patency and the presence of a systemic lytic state. A two tailed p value of <0·05 was regarded as statistically significant.

Table 1 Coagulation variables of all patients stratified according to fibrinolytic state

Variable	*Lytic*	*Non-lytic*	*p value‡*
Fibrinogen (g/l).			
Before	3·1 (0·96)	2·9 (0·48)	NS
90 minutes after	0·0 (0·15)*	2·3 (0·78)†	<0·01
48 h after	2·5 (0·68)*	4·2 (0·84)	<0·01
Plasminogen (%)			
Before	97 (18)	104 (6)	NS
90 min after	11 (13)*	57 (9)*	<0·01
48 h after	55 (13)*	78 (12)†	<0·01
α_2 antiplasmin (%).			
Before	93 (14)	90 (12)	NS
90 min after	4 (5)*	35 (2)†	<0·01
48 h after	80 (16)*	99 (8)	<0·01
Reptilase time (s)			
Before	19 (10–27)	19 (18–20)	NS
90 min after	109 (44–201)*	24 (18–31)	<0·01
48 h after	19 (15–23)	20 (19–21)	NS
Euglobulin clot lysis time (min).			
Before	>120 (>120)	>120 (>120)	NS
90 min after	<10 (<10)*	<10 (<10–15)†	NS
48 h after	>120 (95–>120)	>120 (>120)	NS
Fibrinogen/fibrin products (μg/l)			degradation
Before	<8 (<8)	<8 (<8)	NS
90 min after	>256 (<8–>256)*	<8 (<8)	<0·01
48 h after	36 (<8–>256)†	<8 (<8)	<0·05

*p < 0·01 *v* baseline; †p < 0·05 *v* baseline, ‡p value for between group comparison.
Fibrinogen, plasminogen, and α_2 antiplasmin expressed as mean (SD). Values of reptilase time, euglobulin clot lysis time, and fibrinogen/fibrin degradation products as median (range).

Results

COAGULATION DATA

Fifty eight patients were retrospectively classified into two groups. Fifty two showed a systemic fibrinolytic state and in six patients plasma fibrinogen concentrations did not decrease below 1·0 g/l. Initial values of fibrinogen, plasminogen, α_2 antiplasmin, reptilase time, euglobulin clot lysis time, and fibrinogen/fibrin degradation products were similar in the two groups (table 1).

After 90 minutes, fibrinogen, plasminogen, and α_2 antiplasmin concentrations were significantly reduced in both the lytic and non-lytic groups. Mean plasma concentrations of fibrinogen in the lytic and the non-lytic groups were 0·0 g/l and 2·3 g/l (normal range 1·7–3·5); of plasminogen 11% and 57% (normal range 70–130); and of α_2 antiplasmin 4% and 35% (normal range 90–130) respectively. These differences were statistically significant. Individual values for fibrinogen in the six non-lytic patients before and 90 minutes after treatment with anistreplase were: 3·3 *v* 2·7; 2·7 *v* 2·3; 2·4 *v* 1·1; 3·0 *v* 2·2; 2·4 *v* 1·8, and 3·7 *v* 3·6 g/l respectively. The reptilase time was considerably prolonged in the lytic group from 19 to 109 seconds but did not change in the non-lytic group (19 *v* 24 seconds). Euglobulin clot lysis time was shortened from >120 before to <10 minutes after the administration of anistreplase in both groups (normal value >120 minutes). Serum concentrations of fibrinogen/fibrin degradation products remained within normal ranges (<8 μg/ml) in the non-lytic group, whereas they were considerably increased in the lytic group (median value >256 μg/ml).

These changes declined after 48 hours. At that time mean plasma concentrations of fibrinogen, plasminogen, and α_2 antiplasmin were still significantly lower in the lytic group, and, with the exception of fibrinogen, below the normal ranges. Values for reptilase time, euglobulin clot lysis time, and fibrinogen/fibrin degradation products were normal or almost normal.

PATENCY

Ninety minutes after anistreplase administration angiography showed patency in 20 (67%)

Table 2 Relation of coagulation variables to patency of infarct related vessel 48 hours after treatment with anistreplase

	Lytic state	*Non-lytic state*	*p value*
Patency	43	0	0·00012
Non-patency	9	6	
Total	52	6	

of 30 patients. No early reocclusion occurred in these patients. Overall patency at 48 hours was achieved in 43 (74%) of 58 patients. The patency rate was 83% (43/52) in the patients showing a systemic lytic state and 0% (0/6) in those showing a systemic non-lytic state (table 2). The relation between systemic non-lytic state and non-patency of the infarct related vessel was statistically significant ($p < 0·001$).

Discussion

The predictive value of a systemic lytic state for the efficacy of thrombolytic treatment with streptokinase, urokinase, or anistreplase was the subject of several previous studies. White *et al* did not find that systemic haematological markers of fibrinolysis were helpful in explaining the success or failure of intracoronary thrombolysis.[15] In contrast, Rothbard *et al* showed a close relation between a systemic lytic state and reperfusion of the infarct related vessel.[8] Burket *et al* stated that a systemic lytic state, rather than being considered an adverse effect of treatment, might serve as a reasonable clinical goal when thrombolysis is attempted.[16] Lew *et al* showed that high residual fibrinogen concentrations identified patients in whom thrombolytic treatment was relatively ineffective.[17] It is difficult to compare the results of these studies. In the first three studies intracoronary streptokinase or urokinase was given, whereas in Lew *et al's* study streptokinase was administered intravenously. The dosages of streptokinase varied widely as did the interval between onset of chest pain and thrombolytic treatment. Finally, a systemic lytic state was defined differently in these studies—as a reduction in fibrinogen of at least 50%,[15] of at least 10%[8] or to below 0·5 g/l,[17] and Burket *et al* did not define a cut off point.[16] Marder *et al* studied 106 patients treated with streptokinase or anistreplase.[7] A systemic lytic state was defined as a fall of > 20% in plasma fibrinogen concentration. In 4 of the 58 patients treated with 30 U of anistreplase a systemic non-lytic state was found and none of these patients achieved reperfusion. None the less, no statistically significant relation between a systemic non-lytic state and failure of reperfusion was found. In the remaining 48 patients treated with a low dose of intracoronary streptokinase there was also no statistical correlation. Despite the presence of a systemic non-lytic state reperfusion occurred in 10 patients. This discrepancy was partly explained by local thrombolytic effects of intracoronary streptokinase.

In our patients we regarded a systemic lytic state as being likely if the concentration of plasma fibrinogen was <1·0 g/l 90 minutes after the administration of anistreplase. This value was chosen because it is commonly accepted as the haemostatic concentration of fibrinogen.[18] In the lytic group there was an almost complete depletion of fibrinogen, plasminogen, and α_2 antiplasmin, associated with a short euglobulin clot lysis time, considerably prolonged reptilase time, and a high concentration of fibrinogen/fibrin degradation products. In both the lytic and the non-lytic patients there was a comparable shortening of the euglobulin clot lysis time. Euglobulin clot lysis time reflects the fibrinolytic activity of plasma after inhibitors have been removed. Apparently, the fibrinolytic system was activated by anistreplase in all patients. The moderate decrease in plasminogen and α_2 antiplasmin in the non-lytic group also accorded with activation of the fibrinolytic system. Because neither reptilase time nor the concentration of fibrinogen/fibrin products changed, whereas the fibrinogen concentration decreased but remained within normal ranges, it seems likely that inhibition was responsible for the limited expression of fibrinolytic activity.

None of the patients in the non-lytic group showed reperfusion of the infarct related vessel. Thus fibrinolytic inhibition seems to be restricted not only in terms of systemic effects but also for local thrombolytic failure. Initial plasma concentrations of α_2 antiplasmin were similar in both groups. Therefore, it is unlikely that this potent inhibitor is responsible for the supposed fibrinolytic inhibition. Anti-streptokinase antibodies from earlier treatment with streptokinase or anistreplase can be excluded because none of the patients had previously received one of these drugs. There may have been naturally occurring anti-streptokinase antibodies,[19] but they were not sought in our patients.

A systemic non-lytic state 90 minutes after the administration of anistreplase in a proportion of patients with myocardial infarction predicted failure of thrombolysis. The absence of systemic and local fibrinolytic activity was probably due to fibrinolytic inhibitors. These compounds are currently under investigation. The reported findings are relevant not only to explain the mechanism of thrombolytic failure but may also have implications for clinical practice. A simple and rapid laboratory test to detect thrombolytic failure of anistreplase would lead to the option of additional treatment.

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Excess purine degradation caused by an imbalance in the supply of adenosine triphosphate in patients with congestive heart failure

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Abstract

To evaluate purine degradation in patients with congestive heart failure concentrations of serum hypoxanthine, lactate, and noradrenaline were measured before and after submaximal treadmill exercise in 12 patients with chronic congestive heart failure and nine healthy volunteers. In four patients the concentration of hypoxanthine was significantly higher than in the controls or in the remaining eight patients with congestive heart failure. Venous lactate and noradrenaline in the four patients with high concentrations of hypoxanthine were also significantly higher than those in the eight patients with normal concentrations of hypoxanthine. Patients who responded normally were also more likely to have been treated with vasodilators and angiotensin converting enzyme inhibitors. Exercise induced arrhythmias were more common in the patients with high concentrations of hypoxanthine.

These results suggest that the excess purine degradation in patients with congestive heart failure might be the result of a "relative" disturbance in the supply of adenosine triphosphate caused by the shift of cellular metabolism from aerobic glycolysis to anaerobic glycolysis during submaximal exercise and that hypoxanthine (a substrate for xanthine oxidase and a source of free radicals) was increased after submaximal exercise in some patients with congestive heart failure.

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Exercise induces the breakdown of adenosine triphosphate (ATP) and an associated increase in adenosine diphosphate (ADP) and adenosine monophosphate (AMP) in the muscle.[1] Cells try to maintain a high energy charge even if the concentration of ATP falls and the energy level decreases.[2] The formula for energy charge (EC): $EC = ATP + 0{\cdot}5\ ADP/AMP + ADP + ATP$, indicates that a reduction in the concentration of AMP via activation of AMP deaminase, which accelerates purine degradation, will keep the energy charge high during ATP deficiency. The cells, however, can meet energy demands by producing ATP through aerobic glycolysis or creatinine phosphate. The ATP produced blocks AMP deaminase allosterically and increases purine degradation. Excess purine degradation in the muscle was reported in glycogen storage disease of types III, V, and VII.[3] In these patients an "absolute" disturbance in the supply of ATP from glycogenolysis or glycolysis during exercise facilitated the breakdown of ATP and/or increased ADP and AMP, resulting in an increase in hypoxanthine—that is, urate precursors—by activation of AMP deaminase and accelerated purine degradation. In patients with hyperthyroidism[4] we found that a "relative" disturbance of ATP supply—that is the demand for ATP exceeded its supply—also induced the excess purine degradation in skeletal muscle.

We now report excess purine degradation induced by submaximal treadmill exercise in some patients with congestive heart failure. We believe that the increase in serum hypoxanthine in these patients may have been related to a "relative" disturbance in the supply of ATP during submaximal exercise which may be partly the result of a shift in cellular metabolism in the muscles from aerobic glycolysis to anaerobic glycolysis.

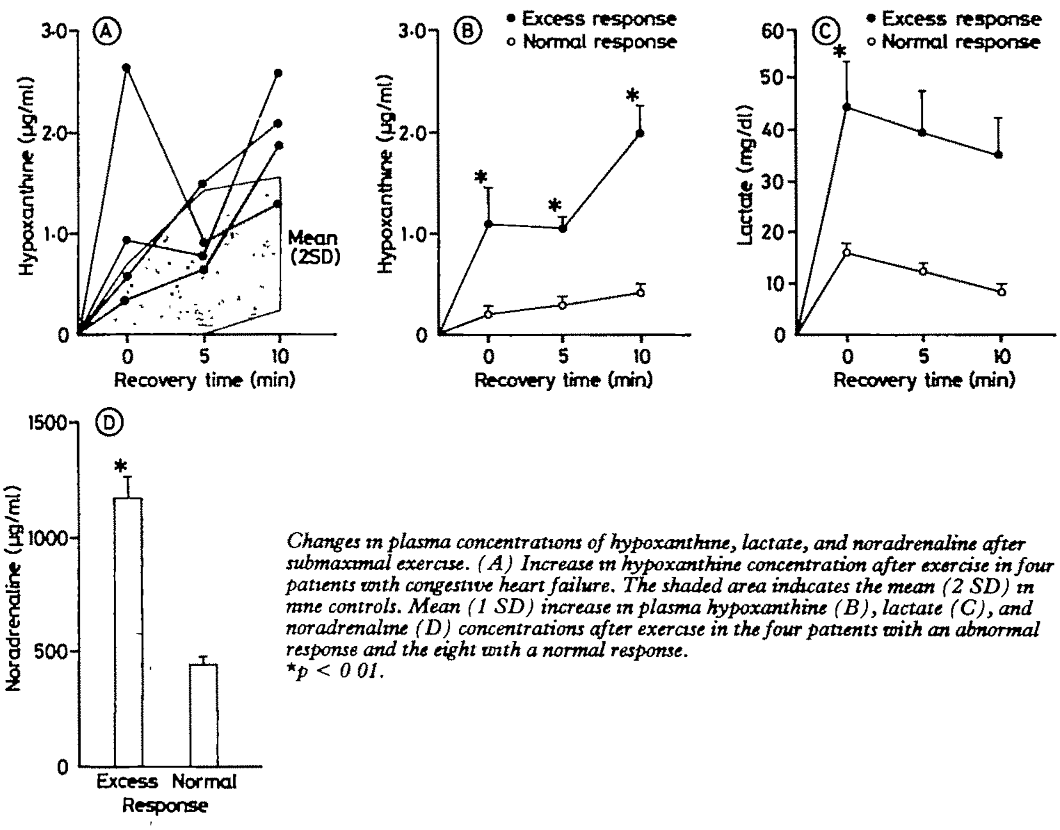
Patients and methods

We studied 12 patients with chronic, stable, congestive heart failure class II and nine healthy volunteers. Subjects exercised on a treadmill according to the modified Bruce protocol. They stopped exercising when they achieved 85% of their calculated maximal predicted heart rate without becoming short of breath or fatigued.

To investigate purine degradation we collected venous blood specimens through a catheter in the antecubital vein to measure serum lactate, hypoxanthine, and noradrenaline, creatinine, and creatine kinase after 15 minutes' bed rest, immediately after the end of exercise, and 5 and 10 minutes after the end of an exercise test with 3 minute stages. Blood lactate was measured enzymatically. Hypoxanthine and noradrenaline were measured by high performance liquid chromatography.

Results

Figure A shows the changes in hypoxanthine from basal concentration—that is the concentration at rest—in four patients with congestive heart failure after a submaximal treadmill exercise test. The shaded area shows the mean (2 SD) increase in plasma hypoxanthine in nine healthy individuals after a submaximal exercise test. In four patients with congestive heart failure plasma concentrations of hypox-



Changes in plasma concentrations of hypoxanthine, lactate, and noradrenaline after submaximal exercise. (A) Increase in hypoxanthine concentration after exercise in four patients with congestive heart failure. The shaded area indicates the mean (2 SD) in nine controls. Mean (1 SD) increase in plasma hypoxanthine (B), lactate (C), and noradrenaline (D) concentrations after exercise in the four patients with an abnormal response and the eight with a normal response.
$^{*}p < 0{\cdot}01$.

Clinical characteristics of patients with congestive heart failure in patients with an abnormal hypoxanthine response and a normal response

					Arrhythmia	
Group	*Patient*	*Age and sex*	*Diagnosis*	*Treatment*	*Rest*	*Exercise*
Raised plasma hypoxanthine:	1	61 F	OMI	Dig, ca, diu	(—)	SVPC (+) VPC (+)
	2	55 F	MS	(—)	(—)	SVPC (+)
	3	40 M	MR	(—)	(—)	SVPC (+) VPC (+)
	4	51 M	OMI	Dig	(—)	(—)
Normal plasma hypoxanthine:	5	56 F	MSR	Dig	SVPC (+)	SVPC (+)
	6	74 F	MSR + ASR	Dig, diu, nitrate	VPC (+)	VPC (+)
	7	50 M	OMI	Dig, diu, nitrate, ACEI	(—)	VPC (+)
	8	64 F	ASR + MSR	Dig, diu	VPC (+)	VPC (+)
	9	62 F	HTH	Ca	VPC (+)	VPC (−)
	10	59 F	IHD	Dig, diu, nitrate, ACEI	(—)	(—)
	11	40 F	MS, AR	Dig, diu	(—)	(—)
	12	44 M	ASD	(—)	SVPC (+)	(—)

ACEI, ACE inhibitor, AR, aortic regurgitation; ASR, aortic stenosis and regurgitation; ASD, atrial septal defect, Ca, calcium antagonist, Dig, digitalis, diu, diuretics, HTH, hypertensive heart disease; IHD, ischaemic heart disease; MR, mitral regurgitation, MS, mitral stenosis, MSR, mitral stenosis and regurgitation; OMI, old myocardial infarction; SVPC, supraventricular premature contraction; VPC, ventricular premature contraction.

anthine were considerably increased after submaximal exercise. In the remaining eight patients they were not significantly different from concentrations in the healthy volunteers (fig B). In the four patients with increased concentrations of serum hypoxanthine and the eight with normal concentrations the exercise test was stopped when they reached 85% of the maximum predicted heart rate without symptoms. The mean (SD) duration of exercise was similar in both groups (7·0 (1·3) minutes in patients with a high concentration and 6·9 (1·7) minutes in patients with a normal concentration of hypoxanthine. Figures C and D show that increases in lactate and noradrenaline from basal concentrations were significantly higher in patients with high hypoxanthine concentrations after submaximal treadmill exercise than in those with normal concentrations.

The table shows the clinical characteristics of all the patients with congestive heart failure. The range of diagnoses was similar in patients with an increased concentration of serum hypoxanthine after submaximal exercise and those without, and the mean ejection fraction of the left ventricle in the two groups was similar too (54·3% and 53·2% respectively). Only one of the four patients with high hypoxanthine concentrations was taking vasodilators and none of them was taking an angiotensin converting enzyme inhibitor. However, four of the eight patients with a normal hypoxanthine response were taking a vasodilator and two others were taking an angiotensin converting enzyme inhibitor.

When we remeasured the hypoxanthine response in patient 2 after percutaneous balloon dilatation of the mitral valve the serum hypoxanthine concentration was normal.

Three of the four patients with high concentrations of serum hypoxanthine had exercise induced arrhythmias whereas only one of the eight patients with a normal hypoxanthine response had exercise induced arrhythmia.

Discussion

We showed that the plasma concentration of hypoxanthine was increased after submaximal treadmill exercise in some patients with congestive heart failure. Concentrations of blood lactate and plasma noradrenaline were also increased in these patients. Exercise increased plasma hypoxanthine in glycogen storage disease types III, V, VII[3] and hyperthyroidism[4] and this increase in hypoxanthine was associated with excess purine degradation. These findings suggested that hypoxanthine was a good index of purine degradation via the purine nucleotide cycle, because increased AMP deamination via activation of AMP deaminase could accelerate the subsequent breakdown of inosine monophosphate to inosine, thereby leading to the formation of hypoxanthine. So the abnormal increase in plasma hypoxanthine in four of our patients with congestive heart failure may reflect the activation of the purine nucleotide cycle in the skeletal muscle. Theoretically, plasma purine concentrations may be raised by increased production or decreased renal clearance of these compounds.[5] Plasma hypoxanthine concentrations could have been increased by the hyperpermeability of the cell membrane or decreased renal clearance of hypoxanthine. But concentrations of creatine kinase and creatinine were similar before and after the exercise test (not shown) and other reports[5,6] suggest that the increase in the concentration of hypoxanthine was probably caused by increased synthesis, with some contribution from impaired renal clearance.

The possible mechanisms of excess purine degradation in the skeletal muscle after submaximal treadmill exercise are: (*a*) an "absolute" disturbance of the supply of ATP caused by deficient glycogenolysis or glycolysis; or (*b*) a "relative" disturbance in the supply of ATP—that is, the demand for ATP exceeds its supply. Where there was an absolute disturbance, such as in glycogen storage disease, there was no accompanying increase in lactate[3]; but a relative disturbance, such as in hyperthyroidism, was associated with an increase in lactate.[4] In our study, an increase in plasma hypoxanthine was accompanied by an increase in plasma lactate. Thus excess purine degradation in our patients could have been the result of a "relative" disturbance in the supply of ATP—that is when the demand for ATP exceeded its supply during exercise, because during submaximal exercise glycolysis became anaerobic and much less efficient than aerobic glycolysis at generating ATP. Excess purine degradation was also accompanied by an increase in plasma noradrenaline. In an earlier study there was an inverse correlation between plasma noradrenaline and pulmonary artery oxygen saturation, showing that the response of the sympathetic nervous system changed to meet the oxygen demand of working skeletal muscle.[7] The excess purine degradation in our patients might be related to the "relative" disturbance in the supply of ATP in the working muscle caused by the cell energy crisis[8] precipitated by hypoxia during exercise. The rise in plasma hypoxanthine concentrations may be a good index of a deficiency of energy in the cell during exercise caused by insufficiency of the peripheral circulation in patients with congestive heart failure.

This hypothesis accords with the finding that plasma concentrations of hypoxanthine were much less likely to be high in patients treated with angiotensin converting enzyme inhibitors and vasodilators. In one patient a high plasma concentration of hypoxanthine in response to exercise was abolished by percutaneous balloon dilatation of the mitral valve.

Hypoxanthine can cause direct tissue injury. The enzyme xanthine oxidase converts hypoxanthine to xanthine and uric acid. Release of oxygen metabolites during this oxidation process peroxidises the cell membrane. We found that hypoxanthine, a substrate for xanthine oxidase, was increased after submaximal exercise in some patients with congestive heart failure. Could direct tissue injury by increased hypoxanthine lead to arrhythmia? Certainly, exercise induced arrhythmia was more common in the patients with high plasma hypoxanthine concentrations than in those without. The possibility of a relation between increased plasma hypoxanthine and exercise induced arrhythmia should be investigated.

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Dipyridamole magnetic resonance imaging: a comparison with thallium-201 emission tomography

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Abstract

Limitation of space and motion artefact make magnetic resonance imaging during dynamic exercise difficult. Pharmacological stress with dipyridamole can be used as an alternative to exercise for thallium scanning. Forty patients with a history of angina and an abnormal exercise electrocardiogram were studied by dipyridamole thallium myocardial perfusion tomography and dipyridamole magnetic resonance wall motion imaging with a cine gradient refocused sequence. Images for both scans were obtained in the oblique horizontal and vertical long axis and short axis planes before and after pharmacological stress with dipyridamole. The myocardium was divided into nine segments for direct comparison of perfusion with wall motion. Segments were assessed visually into grades—normal, hypokinesis or reduced perfusion, and akinesis or very reduced perfusion. After dipyridamole there were reversible wall motion abnormalities in 24 (62%) of 39 patients with coronary artery disease and 24 (67%) of 36 patients with reversible thallium defects. The site of wall motion deterioration was always the site of a reversible thallium defect. Thallium defects affecting more than two segments were always associated with wall motion deterioration but most single segment thallium defects were undetected by magnetic resonance imaging. There was a significant correlation between detection of wall motion abnormality, the angiographic severity of coronary artery disease, and the induction of chest pain by dipyridamole. There were no significant differences in ventricular volume or ejection fraction changes after dipyridamole between the groups with and without detectable reversible wall motion changes but the normalised magnetic resonance signal intensity of the abnormally moving segments was significantly less than the signal intensity of the normal segments. In nine patients the change was apparent visually and it was maximal in the subendocardial region.

Magnetic resonance imaging of reversible wall motion abnormalities in patients with coronary artery disease is feasible during pharmacological stress with dipyridamole and may be associated with a reduced magnetic resonance signal. The failure to show wall motion abnormalities in all cases of reversible thallium defects may be because the defect was small or because dipyridamole caused perfusion defects in the absence of myocardial ischaemia.

Magnetic resonance imaging of the cardiovascular system yields both anatomical and functional information with clarity and accuracy, but its application in patients with coronary artery disease has been limited by the difficulty of imaging during dynamic exercise.[1] Pharmacological intervention with dipyridamole offers a potential solution, and its use in combination with thallium-201 scintigraphy is well established as a method of assessing the impairment of myocardial perfusion in territories served by diseased coronary arteries.[2] Echocardiography[3] and radionuclide ventriculography[4] showed that the inequalities of perfusion induced by dipyridamole may be sufficient to produce myocardial ischaemia and regional wall motion abnormalities, though the reported incidence of such changes is variable.[5 6] We therefore wanted to establish the feasibility of magnetic resonance imaging after intravenous dipyridamole and to investigate the relation between inequalities of myocardial perfusion shown by thallium-201 emission tomography and wall motion abnormalities shown by cine magnetic resonance imaging.

Patients and methods

We studied 40 patients (33 men and seven women aged 35–75 (mean 54)) with a history of chest pain and an abnormal exercise electrocardiogram. Twenty three patients had had a previous myocardial infarction. Magnetic resonance imaging and thallium-201 myocardial perfusion imaging were performed in all patients in the two days before coronary arteriography and there were no significant clinical events in the period between imaging and arteriography. Nine patients had three vessel disease, 21 two vessel disease, nine one vessel disease, and one patient had normal coronary arteries. Angina medication was stopped at least 12 hours before each study as was consumption of beverages containing caffeine (tea, coffee, cocoa). None of the patients had a history of bronchospasm and none was taking aminophylline or related drugs. Each patient gave informed consent and the study was approved by the hospital ethics committee.

MAGNETIC RESONANCE IMAGING

Cine magnetic resonance imaging was performed with a Picker International MR2055 scanner operating at 0·5 T. Blood pressure was monitored by an automatic pneumatic cuff system and intravenous access was established through an indwelling cannula connected to fine bore tubing. The electrocardiogram was recorded in the normal way with lead CM5. We used a field even echo rephasing (FEER) sequence for cine imaging[7] in the vertical long axis, horizontal long axis, and apical and basal short axis planes. The echo time of the sequence was 14 ms and the repetition time was adjusted to acquire 16 images spanning all but the final 60 ms of diastole. The field of view was 45 cm, slice thickness was 10 mm, and two acquisitions of 128 phase encoding steps were averaged. The images were interpolated from 128 × 256 pixels to 512 × 512 for display.

After acquisition of the initial images and without removing the patient from the magnet, dipyridamole was infused at a rate of 0·142 mg/kg/minute for four minutes. In the absence of significant symptoms or a fall in mean blood pressure of more than 20 mm Hg, a further 10 mg bolus was given at 10 minutes to maintain effects on wall motion. At the end of the infusion cine imaging was repeated in the same planes as before the infusion. The scanning time before dipyridamole was given was approximately 30 minutes including pilot images but after dipyridamole was given scanning time was shorter because of the increase in heart rate, and it was typically 15–20 minutes.

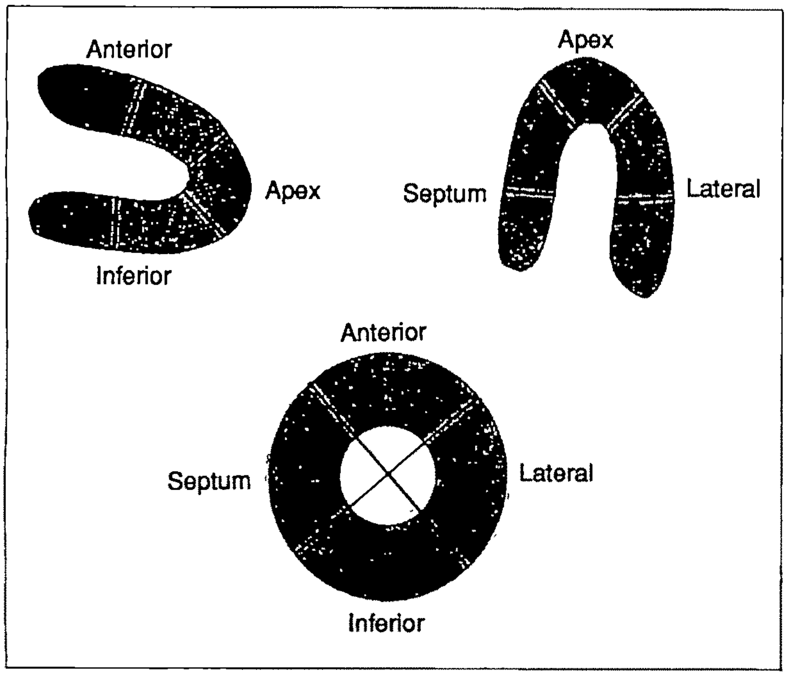


Figure 1 Diagram showing oblique imaging planes through the left ventricle. Vertical long axis (top left), horizontal long axis (top right), and short axis (bottom). The four walls were divided into apical and basal segments which with the apex produced a total of nine segments for analysis. Short axis images were acquired through the apical and basal parts of the ventricle so that each segment was seen independently in two different planes.

THALLIUM-201 MYOCARDIAL PERFUSION IMAGING

Dipyridamole was infused intravenously at a rate of 0·142 mg/kg/minute for four minutes followed by 80 MBq of thallium-201 four minutes from the end of the infusion. Emission tomographic imaging was started four minutes later with a General Electric 400AZS gamma camera and a General Electric Star computer system. Thirty two planar images (64 × 64 pixel matrix, 400 mm field of view, 30 s per image) were acquired over a 180° arc from the right anterior oblique position to the left posterior oblique position. Redistribution images were acquired after four hours in an identical manner. The planar images were reconstructed into transaxial tomograms of one pixel depth by back projection and a Ramp-Hanning filter with a 0·75/pixel cut off frequency. From the transaxial tomograms, oblique images were reconstructed in the vertical long axis, horizontal long axis, and short axis planes.

CORONARY ARTERIOGRAPHY

Judkins's technique was used with multiple views of each vessel, and contrast left ventriculography was performed in the right anterior oblique projection.

IMAGE ANALYSIS

All images were assessed independently by two experienced observers without knowledge of the results of other investigations. Disagreements were resolved by discussion. The tomograms were divided as shown in fig 1. Wall motion in each segment on the cine magnetic resonance tomograms was classed as normal, hypokinetic, or akinetic and myocardial perfusion was classed on the thallium-201 tomograms as normal, reduced, or absent. Because each segment of the myocardium was seen in two different planes, a total of nine segments was assessed and if the appearance of a segment differed between planes, the worse of the two classifications was used. A wall motion abnormality induced by dipyridamole was defined as a deterioration of at least one category and this finding was called a positive magnetic resonance scan. Dipyridamole induced ischaemia was defined as impaired perfusion with redistribution of at least one category in the delayed thallium-201 images. A significant coronary stenosis was defined as a reduction of at least 50% of the normal luminal diameter. Left ventricular end diastolic and end systolic volumes were calculated from the vertical and horizontal magnetic resonance tomograms by a biplane area-length technique.[8] Stroke volume and ejection fraction were derived.

STATISTICAL ANALYSIS

Myocardial magnetic resonance signal levels and haemodynamic and ventricular volume differences before and after dipyridamole

Table 1 Haemodynamic changes before and after intravenous dipyridamole given during magnetic resonance imaging

	Before	*After*	*Change (CI)*	*p*
Positive scan (n = 24):				
Systolic BP (mm Hg)	134	133	−1 (−6, +3)	NS
Diastolic BP (mm Hg)	79	76	−3 (−6, 0)	NS
Heart rate (beats/min)	67	85	18 (+13, +23)	<0·001
Rate × pressure (mm Hg/min)	8955	11240	2285 (+1544, +3344)	<0·001
Negative scan (n = 16)				
Systolic BP (mm Hg)	131	136	5 (−5, +14)	NS
Diastolic BP (mm Hg)	77	75	−2 (−6, +3)	NS
Heart rate (beats/min)	61	77	16 (+12, +19)	<0·001
Rate × pressure (mm Hg/min)	8047	10402	2355 (+1418, +3356)	<0·001

Mean values are given in each group and the mean changes with 95% confidence interval (CI).
BP, blood pressure

Table 2 Side effects and clinical observations after intravenous dipyridamole in 40 patients

Side effect	*Number*	*(%)*
Chest pain	27	68
Headache	12	30
Facial flushing	6	15
Dyspnoea	4	10
Nausea	3	8
Arrhythmia	3*	8
Tiredness	2	5
Perineal flushing	1	3
Felt unwell	1	3
Legs numb	1	3

*Ventricular extrasystoles 1, atrial extrasystoles 1, bigeminy 1.

were compared by Student's paired *t* test, with a logarithmic transformation for the double product data to achieve a normal distribution. Differences between groups were compared by a test of covariance. The χ^2 test was also used where appropriate. A probability <0·05 was considered significant.

Results

CLINICAL EFFECTS OF DIPYRIDAMOLE

Table 1 shows the haemodynamic response to dipyridamole infusion during magnetic resonance imaging divided according to whether a new wall motion abnormality was seen (positive magnetic resonance scan) or not seen (negative scan). There were no significant differences between the two groups in any variable before dipyridamole and there were no significant changes in blood pressure after dipyridamole. The heart rate and double product increased significantly after dipyridamole but there was no difference in the response between groups with positive and negative scans.

Table 2 summarises the side effects experienced by the patients. Six patients (15%) had no symptoms, 19 (48%) had non-cardiac side effects, and 27 (68%) had cardiac side effects, the commonest of which was chest pain which occurred in all 27 patients (68%) sometimes with dyspnoea. In none of these was the chest pain severe and only one patient was given aminophylline because of nausea. The chest pain occurred between one and four minutes after the end of the dipyridamole injection and persisted for up to 10 minutes. When a further 10 mg bolus of dipyridamole was given at 10 minutes, this invariably worsened the discomfort. Arrhythmias occurred in only three (8%) patients and they were unsustained and of no haemodynamic importance. Two of these patients had two vessel coronary disease with reversible ischaemia of one and four segments on thallium imaging and the third patient had normal coronary arteries, suggesting that there was no relation between arrhythmia and the severity of coronary disease.

WALL MOTION BY MAGNETIC RESONANCE IMAGING

The quality of the cine images before dipyridamole infusion was adequate for the analysis of wall motion in all patients but, as previously observed,[9] the contrast between blood and the myocardium was better in the two short axis planes. The lower contrast in the long axis planes complicated the measurement of left ventricular volume particularly at end systole. Image quality was poorer in some patients after dipyridamole, especially in those in whom chest pain and tachypnoea developed, but in no case did this interfere with the interpretation of stress wall motion.

In all of the 23 patients with previous myocardial infarction, regional abnormalities of wall motion, wall thinning, or both were seen (fig 2). The site of these abnormalities accorded closely with the electrocardiogram, thallium-201 myocardial perfusion imaging, and *x*-ray ventriculography. Wall motion was normal before dipyridamole in the patients without

Table 3 Relation between the number of diseased coronary vessels and the likelihood of a wall motion abnormality induced by dipyridamole (positive MR)

	No of diseased vessels			
	0	*1*	*2*	*3*
Negative MR	1	7	8	0
Positive MR	0	2	13	9

$\chi^2 = 12·9$; $p < 0·01$

Table 4 Induction of chest pain by dipyridamole as a predictor of the development of a new wall motion abnormality

	No chest pain	*Chest pain*
No new wall motion abnormality	11	5
New wall motion abnormality	2	22

$\chi^2 = 13·3$, $p < 0·001$

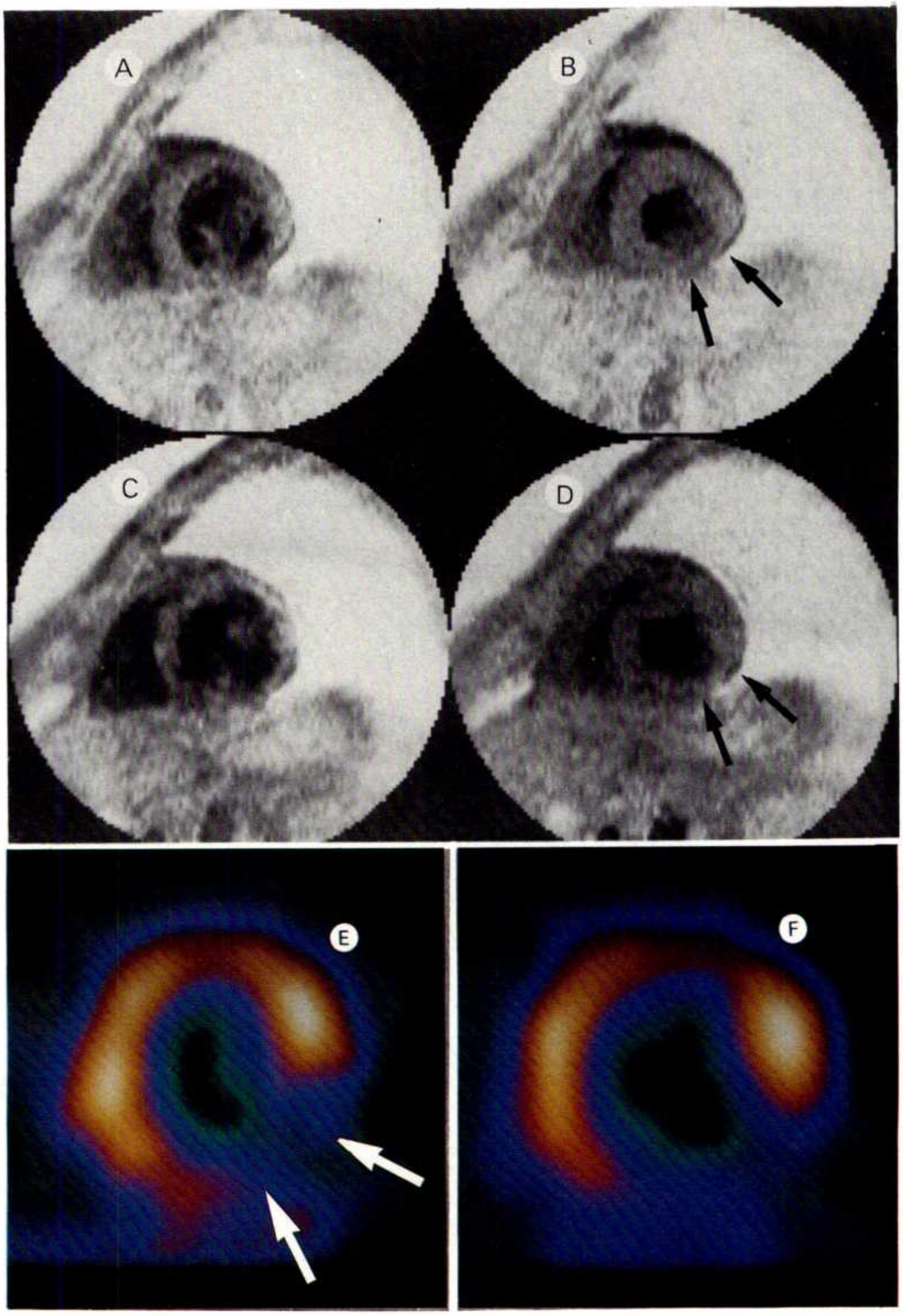


Figure 2 Magnetic resonance and thallium-201 images of infarction without reversible ischaemia. The magnetic images show (A and B) end diastolic and end systolic frames before the infusion of dipyridamole and (C and D) after the infusion of dipyridamole. The arrows in B indicate an area of myocardium in the inferolateral wall that was thinned and did not contract normally. There was no change after dipyridamole stress (D). The site accorded with the non-reversible defect in the stress (E) (arrowed) and redistribution (F) thallium short axis tomogram. The patient had an occluded left circumflex artery with infarction.

previous infarction, though there was some normal variation with apparent hypokinesis in the region of the membranous septum and some apical thinning and hypokinesis.

After infusion of dipyridamole wall motion deteriorated by at least one grade in at least one segment in 24 (60%) patients (fig 3). Of these, 10 had normal wall motion before dipyridamole but 14 patients did not. In these patients with previous infarction, the new abnormality occurred in a normal region in seven, in an already abnormal region in four (hypokinesis became akinesis), and in both normal and abnormal regions in three. The new wall motion abnormalities always occurred in the territory of an abnormal coronary artery and their site accorded closely with the site of a reversible thallium-201 defect, although the wall motion abnormality was often smaller. Of the 16 patients (40%) without a wall motion abnormality induced by dipyridamole, nine had previous myocardial infarction with ab-

Table 5 Relation between the number of segments with reversible defects of thallium-201 uptake induced by dipyridamole and likelihood of a new wall motion abnormality

	Negative MR	*Positive MR*
0–2 Segmental thallium defects	16	8
3–9 Segmental thallium defects	0	16

$\chi^2 = 15.1$; $p < 0.001$.

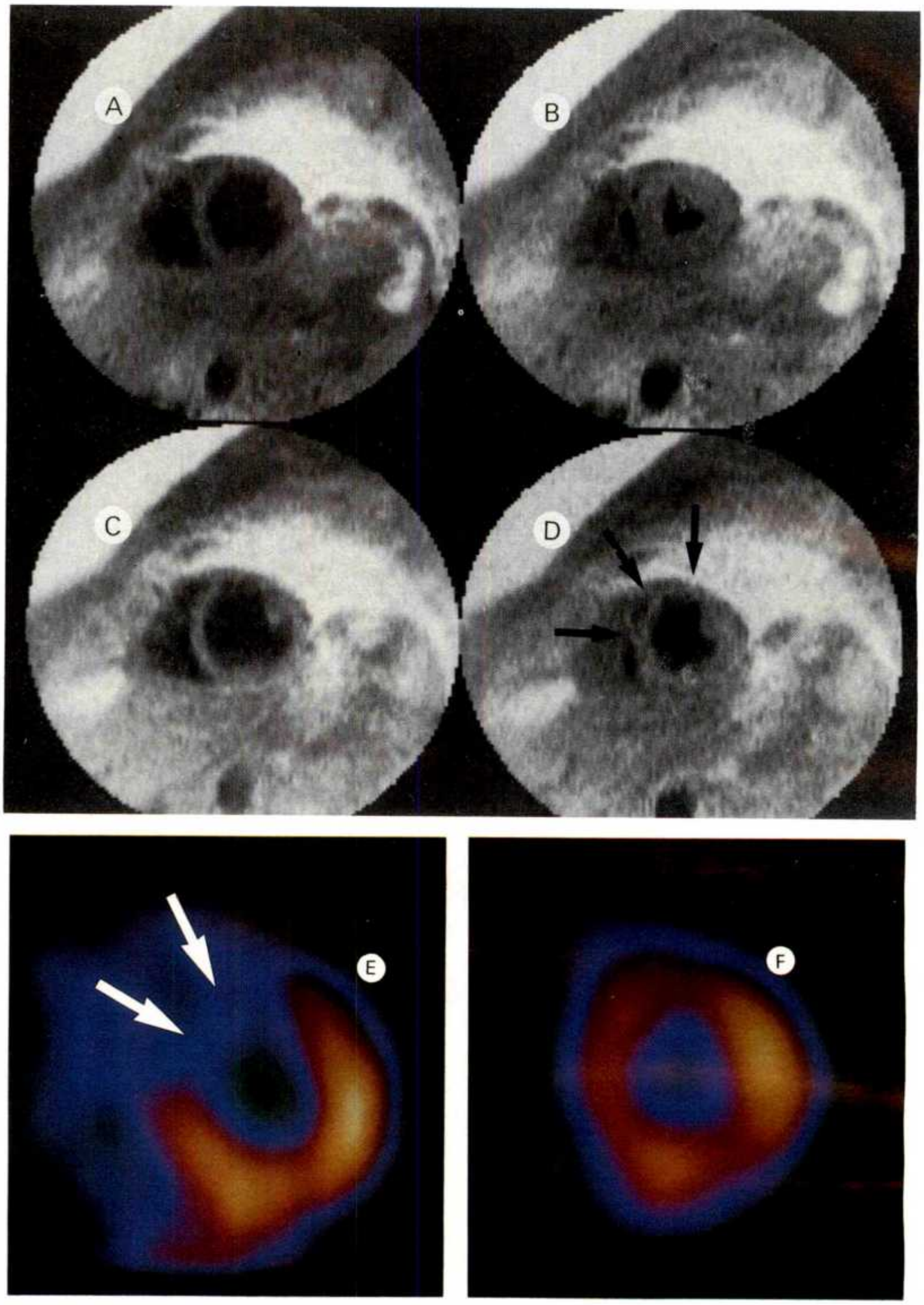


Figure 3 Magnetic resonance and thallium-201 images of reversible ischaemia. The magnetic resonance images show (A and B) end diastolic and end systolic frames before the infusion of dipyridamole and (C and D) after the infusion of dipyridamole. The pattern of contraction was normal with uniform systolic thickening before infusion of dipyridamole (B). The end systolic frame after dipyridamole (D) was abnormal with impaired extent of contraction in the anteroseptal region (black arrows). The site accorded with that on the stress thallium short axis tomogram (E) (white arrows). The redistribution thallium tomogram (F) showed complete reperfusion. The patient had an occluded left anterior descending artery with no evidence of infarction.

normal wall motion and seven had normal wall motion.

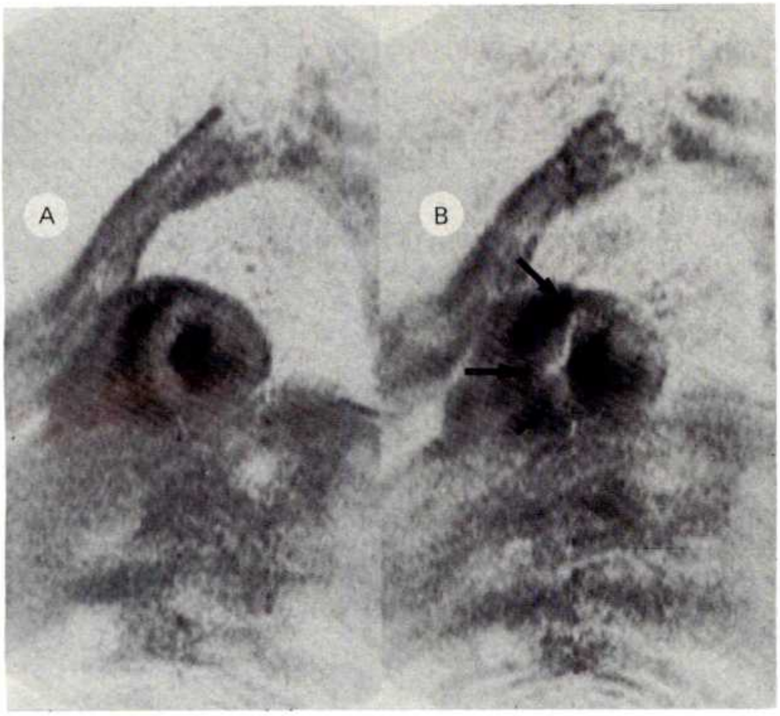
There was a strong relation between the extent of coronary artery disease and the likelihood of a wall motion abnormality being induced by dipyridamole (table 3). Similarly, the development of chest pain after dipyridamole was a good predictor of the presence of a new wall motion abnormality (table 4). One of the two patients with a new wall motion abnormality but no chest pain had insulin dependent diabetes mellitus with a peripheral neuropathy.

Table 6 Mean left ventricular volumes before and after dipyridamole in the groups of patients with (positive MRI) and without (negative MRI) wall motion abnormalities induced by the infusion

	Before	*After*	*Change (95% CI)*
Positive MRI:			
End diastolic volume (ml)	146	138	−8 (−20, +4)
End systolic volume (ml)	65	61	−4 (−10, +2)
Stroke volume (ml)	81	77	−4 (−15, +7)
Ejection fraction (%)	57	58	+1 (−3, +5)
Negative MRI:			
End diastolic volume (ml)	132	130	−2 (−11, +8)
End systolic volume (ml)	52	47	−5 (−14, +4)
Stroke volume (ml)	80	83	+3 (−9, +16)
Ejection fraction (%)	61	64	+3 (−3, +9)

THALLIUM-201 MYOCARDIAL PERFUSION IMAGING

Of the 23 patients with previous myocardial infarction, all had defects of thallium-201 uptake in the redistribution images, and 20 had additional reversible defects induced by dipy-



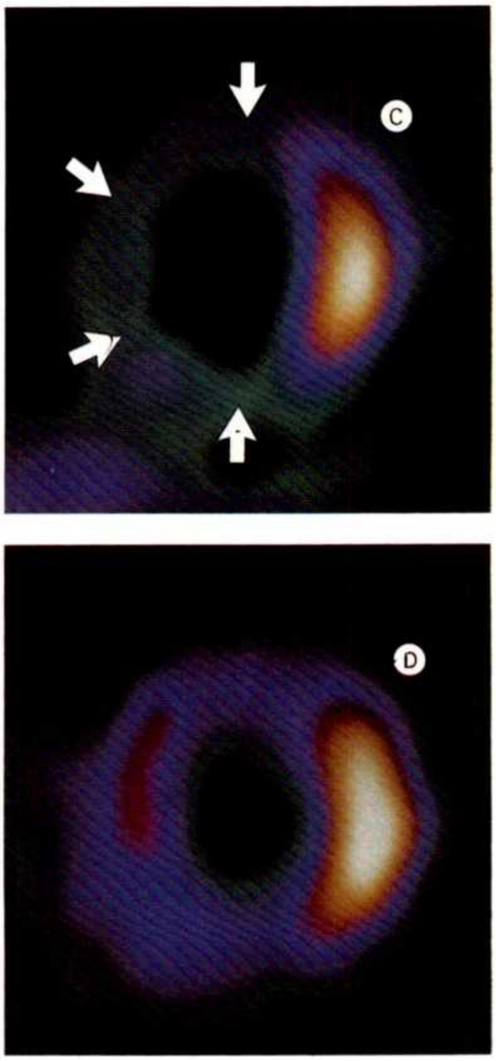


Figure 4 Magnetic resonance image with subendocardial signal change. The magnetic resonance images (reverse video format) show end systolic frames (A) before and (B) after dipyridamole. The cine display showed delayed septal contraction. A considerable decrease in the signal intensity of the septum was also visible which extended from the anterior wall to mid-septum (large black arrows) and continued down the inferior septum (small black arrow) apparently in the subendocardium. The stress thallium short axis tomogram (C) showed the corresponding extensive anterior, septal, and inferior wall perfusion deficit (short white arrows) that became partially reperfused (D). It is likely that 24 hour delayed redistribution imaging would show further reperfusion in these segments. The patient had diseased left anterior descending and right coronary arteries.

ridamole, of which 14 were new defects and six were a deterioration of a pre-existing abnormality. Of the 17 patients without previous infarction, all had normal redistribution images and 16 had new abnormalities induced by dipyridamole. The patient with a normal thallium-201 scan had normal coronary arteries.

There was a strong correlation between the number of reversible thallium-201 defects and the likelihood of a new wall motion abnormality seen by magnetic resonance (table 5). Defects larger than two segments were always associated with reversible wall motion abnormalities. Of the 16 negative magnetic resonance scans, 12 had reversible defects smaller than two segments, while only two of the positive magnetic resonance scans had perfusion defects smaller than two segments.

VENTRICULAR VOLUMES AND EJECTION FRACTION

Table 6 shows the changes in end diastolic left ventricular volume, end systolic volume, stroke volume, and ejection fraction. There was no significant difference between the values before dipyridamole infusion in patients with new wall motion abnormalities or without, and though there was a trend towards a decrease in volumes after dipyridamole in both groups, covariance analysis showed no differences between groups.

MAGNETIC RESONANCE SIGNAL CHANGES IN THE MYOCARDIUM

The myocardial signal in the magnetic resonance images was normalised to alterations in signal from fat, to correct for changes arising from different acquisition variables before and after dipyridamole infusion (table 7). There was a small increase in signal after dipyridamole, both in the segments with normal perfusion and in those with reversible perfusion defects, but the changes were not statistically significant and there was no difference between these two groups. Not all of the segments with reversible perfusion defects had wall motion abnormalities, however, because after dipyridamole thallium defects can occur without ischaemia. There was a significant fall in signal in segments with new wall motion abnormality and an increase in signal in adjacent segments with normal wall motion ($p < 0.05$) (table 8). In nine of the 24 patients with new wall motion abnormalities, the abnormally low signal was

Table 7 Mean change in magnetic resonance signal after dipyridamole in areas with reversible perfusion defects and normal myocardium

Normalised MR signal	*Before dipyridamole*	*After dipyridamole*	*Change (95% CI)*	*p*
Reversible perfusion defect	540	554	+14* (−27, +55)	NS
Normal perfusion	528	538	+10* (−13, +32)	NS

*p = NS.

Table 8 Mean change in magnetic resonance signal after dipyridamole in myocardium with a reversible wall motion abnormality and in normal myocardium

Normalised MR signal	*Before dipyridamole*	*After dipyridamole*	*Change (95% CI)*	*p*
Abnormal wall motion	543	530	−13* (−2, −26)	<0·05
Normal wall motion	519	531	+12* (−7, +30)	NS

*p < 0·05. In nine patients the signal reduction was visible on the images.

apparent from inspection of the images and it was most pronounced in the subendocardium (fig 4). The patients with visible abnormalities of magnetic resonance signal had more extensive perfusion defects on thallium imaging, but the numbers were too small for this to be statistically significant.

Discussion

The possibility of combining dynamic exercise with magnetic resonance imaging for the investigation of patients with coronary artery disease has been investigated but it was not possible to acquire diagnostic images at anything other than submaximal exercise because of motion artefact.[1] Very rapid imaging techniques such as echo planar imaging may overcome this problem, but an alternative strategy is to use pharmacological stress. The use of dipyridamole for myocardial perfusion imaging was first established in dog experiments by Gould in 1978[10] and it has since been recognised as a method of inducing defects in thallium-201 images that is at least as reliable as dynamic exercise. The thallium-201 defects do not necessarily correspond with areas of ischaemia, but wall motion abnormalities have been demonstrated by echocardiography[3] and by radionuclide ventriculography[4] and it is reasonable to suppose that there is ischaemia in these cases. We performed the present study to establish the feasibility of dipyridamole magnetic resonance imaging for the investigation of such patients with coronary artery disease; and to investigate the relation between thallium-201 defects induced by dipyridamole and wall motion abnormalities—a relation that has not previously been fully explored.

Dipyridamole acts at the level of the cardiac arteriolar myocyte, where it increases interstitial concentrations of adenosine by the combined effects of inhibition of the facilitated uptake of adenosine and inhibition of its breakdown by adenosine deaminase. Activation of the myocyte membrane purinoceptors leads to an increase of intracellular cyclic adenosine monophosphate and arteriolar vasodilatation.[11] With Gould's original regimen (0·56 mg/kg over 4 minutes)[10] the increase in coronary arterial flow in humans is variable, but it was reported to be between 250%[12] and 600%.[13] The flow reserve is reduced in arteries with fixed stenoses,[14] and the differential flow between territories served by normal and by stenosed arteries may be sufficient to produce an apparent defect of thallium-201 uptake. As we have confirmed, it is also possible to produce ischaemia in the territory of a stenosed artery, and though the mechanisms of this ischaemia are complex there are three possible explanations. Firstly, an increase of flow across a stenosis leads to a fall in distal perfusion pressure which may be sufficient to cause subendocardial ischaemia.[10] Secondly, flow in high resistance collateral vessels serving the area of a diseased artery may be reduced because of the generalised vasodilatation and fall in perfusion pressure. This will be exacerbated by the small reduction in diastolic blood pressure caused by dipyridamole.[15] Thirdly, dipyridamole causes a small increase in the rate-pressure product, mainly because of the reflex tachycardia, which raises myocardial oxygen demand.[15] Techniques such as magnetic resonance imaging which examine regional myocardial function should provide a method of distinguishing between areas of impaired thallium-201 uptake that are relative defects compared with normal areas and those that are associated with sufficient ischaemia to cause wall motion abnormalities.

The use of dipyridamole during magnetic resonance imaging requires that the drug exerts its effect on wall motion over the period of imaging, which is approximately three minutes for a single acquisition but approximately 15 minutes for a complete stress study. Because there is no direct relation between the plasma concentration of dipyridamole and coronary flow we did not measure plasma dipyridamole during the acquisition. The relation between the action of dipyridamole on coronary flow and the consequent myocardial dysfunction is also unclear, but it is reasonable to suppose that the two occur together. Studies of coronary arterial flow in humans suggest that maximal flow occurs about 2½ minutes after the end of infusion[13] and that it continues at close to maximum for a further 9–14 minutes[16] with the half life for flow reduction of approximately 33 minutes.[12] These figures differ from those found by Gould in the dog, where maximal flow increase was seen five minutes after the end of the four minute infusion with peak flow lasting for 3–5 minutes.[10] In addition to the data reported on the time course of flow changes after intravenous dipyridamole it is known that after exercise stress regional wall motion changes persist for up to 20 minutes after the end of exercise.[17,18] For constancy of effects on wall motion, therefore, we decided to administer a further 10 mg bolus of dipyridamole at 10 minutes provided there were no contraindications.

With magnetic resonance imaging we showed reversible wall motion abnormalities after dipyridamole in 24 (62%) of 39 patients with coronary artery disease and 24 (67%) of 36 patients with reversible thallium defects. Studies with other imaging techniques have shown similar results though there is a wide variation in the reported sensitivity for coronary artery disease, varying from 13%[5] to 67%[4] for radionuclide ventriculography, and from 52%[19] to 89%[6] for echocardiography. This may be explained by several factors including the severity of disease in the population studied,[19] the dosage of dipyridamole used,[20] and improvements in imaging techniques.[5,4] There was a close correlation between the site of the induced wall motion defect and the site of the thallium-201 perfusion defect in each patient and this is the first such observation made using equivalent tomographic techniques. A similar observation was made when echocardiography was compared with planar thallium-201 imaging[21] though the differences between the two techniques mean that direct comparison is difficult. By using tomographic techniques we have also shown that the size of the thallium-201 defect is important. All patients without wall motion abnormalities induced by dipyridamole had thallium-201 defects affecting two or fewer segments, while only two patients with wall motion abnormalities had reversible thallium-201 defects affecting less than two segments. There was a similar relation with the number of diseased arteries, in that all patients with three vessel disease had new wall motion abnormalities induced by dipyridamole, while only two of nine patients with single vessel disease had new abnormalities.

We showed a strong relation between the occurrence of chest pain and the development of a wall motion abnormality. This was reported in some studies[19 22] but not in others[20 23] but it is likely that this relation is determined by the severity of disease. Because up to 74% of patients with coronary artery disease do not experience chest pain after dipyridamole infusion[23] and because adenosine is known to cause chest pain in the absence of disease,[24] it seems unlikely that chest pain induced by dipyridamole will be a useful marker of the presence of disease, though it may be a marker of severe disease.

The changes in ventricular volumes and ejection fraction seen in our study are of limited clinical value because of the wide variation and the overlap between patients with and without new wall motion abnormality. In any event, the biplane area-length method that we used assumes that the ventricle is an ellipsoid of revolution and significant errors can be made if this is not the case.[8] Unfortunately, it is more difficult to perform the accurate multislice method of measuring ventricular volume[25] in the limited time available after dipyridamole infusion.

The reduction of magnetic resonance signal seen in nine (41%) of the 22 patients with new wall motion abnormality suggests the possibility of using measurements of myocardial relaxation time to detect ischaemia. Many different factors influence the magnetic resonance signal but, unfortunately, it is unlikely that the observed changes were the results of alterations in relaxation times, because significant changes in T2 were not seen until an hour after experimental coronary occlusion.[26] The altered motion of the abnormal segment might also explain changes in signal; however, hypokinesis would lead to a rise in signal rather than the observed fall. It is most likely that the changes were the result of alterations in the blood content of the myocardium, and this would be supported by the fact that the areas of signal loss were mainly subendocardial where the most severe ischaemia would be expected. Further studies using magnetic resonance contrast agents such as gadolinium diethylenetriamine pentaacetic acid may throw further light on these findings.

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A controlled trial of community based coronary rehabilitation

Hugh J N Bethell, Mark A Mullee

Abstract
Two hundred patients who had suffered an acute myocardial infarction 4–6 weeks before entered a randomised controlled trial of exercise treatment at a community sports centre supervised by a general practitioner. Eighty one per cent of the treatment group continued to exercise until they returned to work and 73% completed three months' exercise. There were no serious complications of the exercise course. The prevalence of angina pectoris fell by 10% in the treatment group but rose by 60% in the control group. The perceived energy level rose by significantly more in the treatment group than in the controls. The rise in predicted maximum oxygen uptake was significantly greater in the treatment group than in the control group as was the reduction in the double product (a reflection of myocardial workload) at peak exercise.

Coronary rehabilitation in the community can be both safe and effective.

The benefits of exercise training for patients with coronary heart disease are widely recognised. Numerous studies of this treatment have shown these effects and the mechanism of their production in selected groups of patients. There have, however, been very few large scale randomised controlled trials in unselected patients recovering from acute myocardial infarction[1–9] and only one in the United Kingdom—and that was hospital based.[6]

The Alton Coronary Rehabilitation Unit (which operates from a community centre and is supervised by a general practitioner, a sports officer, and a physiotherapist) opened in 1976. The purpose of the trial in this unit was to assess the results of managing patients after myocardial infarction.

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Patients and methods

All male patients aged 65 or less admitted to Basingstoke District Hospital from 1 December 1979 with a provisional diagnosis of acute myocardial infarction were recruited to the study. Fasting blood samples taken on the first morning after admission were sent for measurement of cholesterol and triglyceride concentrations. Serial measurements of serum aspartate transaminase activity and electrocardiograms were performed on the first three days of admission. A chest *x* ray was taken within 48 hours of admission. By the fifth day of admission a positive diagnosis of acute myocardial infarction was made only if all of the following criteria were met: a history of chest pain typical of myocardial infarction, progressive electrocardiogram changes, and a rise and fall in aspartate transaminase concentrations with at least one reading above 40 units/ml. Patients were excluded if they lived more than 25 miles from Alton, if they had medical or orthopaedic problems that precluded their taking part in the exercise course, if they had insulin dependent diabetes mellitus or were in atrial fibrillation, if they had previously been through the course, or if they were on the investigator's personal general practice list.

The qualifying patients were randomised by order of admission into treatment and control groups by means of a random letter sequence. The nature of the trial was then explained and the patient was invited to join. At 4–5 weeks after admission all patients were interviewed and examined by one of two research assistants (one a state registered nurse, the other a state registered physiotherapist) who measured height and weight and, with the patient sitting down, recorded resting pulse rate and blood pressure. The patients were asked about symptoms and, if not mentioned specifically, chest pain. The occurrence of tight central chest pain or throat pain brought on by exercise and relieved within a few minutes by rest was recorded as angina. The patients were also asked to express their current well-being and energy level as a percentage of their normal level. One to two weeks later they underwent a submaximal bicycle ergometer exercise test at Alton Sports Centre. Entry to the trial was stopped when 200 patients had been tested. All exercise tests were performed on a mechanically braked Cardionics ergometer with a continuous multistage test with five minutes at each exercise load. The starting load was estimated to allow each patient to complete at least one stage but not more than three stages; the load was increased by 25 W at each level before the end point was reached. The test was terminated when the patient reached 85% of his predicted maximum heart rate, unless it was interrupted by angina pectoris, multifocal ventricular extrasystoles, exhaustion, or excessive breathlessness. Heart rates at the end of the test were calculated from six consecutive complexes on the electrocardiographic write-out (Hewlett-Packard) and for systolic pressure we used a Philips electronic analogue sphygmomanometer calibrated from time to time against a mercury sphygmomanometer. Patients on short acting β blocking drugs stopped taking these drugs 48 hours before the test unless this was contraindicated. We calculated the predicted maximum oxygen uptake ($\dot{V}O_2$ max) from the exercise test using the Astrand-Ryhming nomogram.[10] This could be done only for those who cycled for at least three minutes at their lowest load and for those who were not on β blocking drugs at the time of the test. The double product (heart rate × systolic pressure) at the end of the test was also calculated.

Control patients were given a short talk on the sort of exercise that they might safely take unsupervised. Treatment patients entered a three month course of three times a week circuit training at Alton Sports Centre. The course has been described previously.[11]

Three months from the initial interview the patient was seen again by the research assistant who repeated the initial interview and examination. A second exercise test was performed within the next week, supervised by HJNB, on the same day of the week and at the same time of the day as the first test and with the same protocol.

Mann-Whitney U tests and two-sample t tests were used to test for differences between the two groups (controls and treated) and Wilcoxon signed-rank tests or paired t tests were used to test for differences within the groups. Chi-squared test with Yates's correction factor and McNemar's test were also used when appropriate. Ninety five per cent confidence intervals for χ^2 tests were calculated according to the method described by Armitage and Berry.[12]

Most of the statistical analyses were computed with the statistical packages SPSS-X[13] and Minitab.[14]

Results

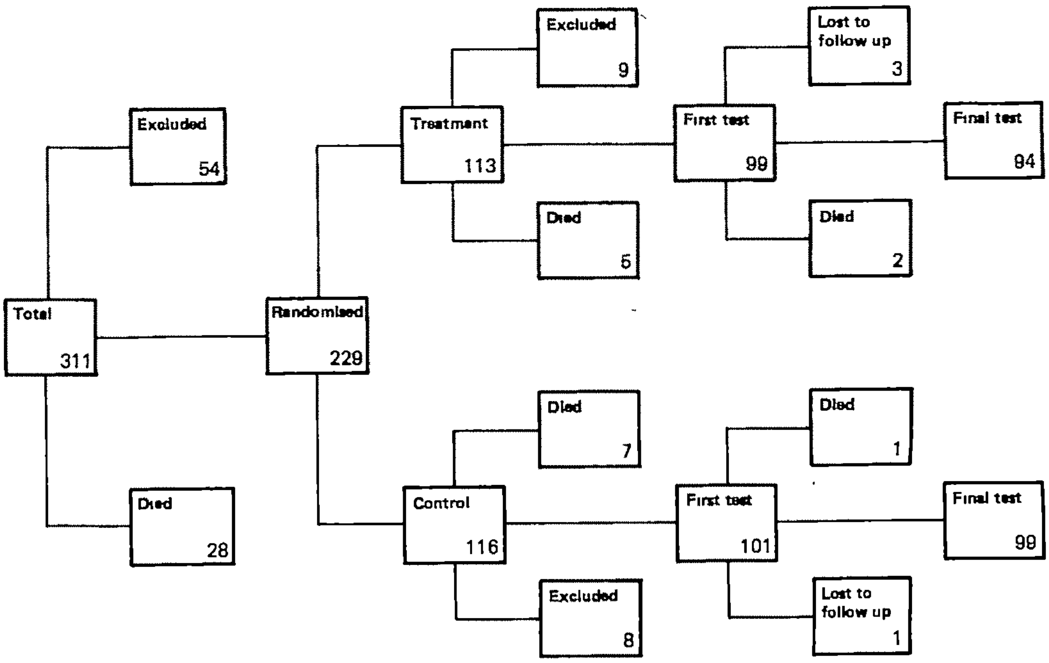
The figure shows the outcome in the 311 male patients aged $\leqslant 65$ who were admitted to the Basingstoke District Hospital Coronary Care Unit between 1 December 1979 and 1 March 1984 with a confirmed diagnosis of acute myocardial infarction. Twenty eight died before randomisation and 54 were excluded for one of the following reasons: geographical (36), medical/orthopaedic contraindications (seven), insulin dependent diabetes mellitus (three), atrial fibrillation (two), previous graduates of the course (three), and on the author's general practice list (three). The remaining 229 were randomised—113 to the treatment group and 116 to the control group. Of the 113 treatment patients, 99 attended Alton Sports Centre for the first exercise test (five died, four refused, and five developed other problems). Of the 116 control patients, 101 attended Alton Sports Centre (seven died, three refused, and five developed other problems). Thus of the 200 patients in the study, 99 were in the treatment group and 101 in the control group, and these patients comprised 85% of the infarct patients who had survived to the time of the first test and lived within 25 miles of Alton.

COMPARABILITY OF GROUPS (TABLES 1 AND 2)

The two groups were comparable in terms of age, presence of Q waves on the electrocardiogram, aspartate transaminase concentration, presence of pulmonary oedema, presence of complications, initial $\dot{V}O_2$ max, and time to return to work.

FOLLOW UP

Of the 99 treatment patients two died and four could not be followed up. One of those patients who died did so between the final interview and the final exercise test and his interview and examination findings are included. Of the re-



Outcome in 311 male patients aged 65 or less who were admitted to the Basingstoke District Hospital coronary unit between 1 December 1979 and 1 March 1984 with a confirmed diagnosis of acute myocardial infarction.

Table 1 Comparability of the two groups

	Mean age (yr) (SD)	Median peak AST (IU/l) (interquartile range)	Pulmonary oedema on chest x ray	Complications*	Mean initial $\dot{V}O_2$ max (ml/min/kg) (SD)	Mean time to return to work (wk) (SD)
Treatment group						
n	99	99	99	99	78	63
	54 2 (7 2)	202 (122, 327)	11%	27%	22 2 (5·0)	13 7 (3·7)
Control group						
n	101	101	100	101	80	66
	53·2 (7 7)	207 (114, 302)	11%	27%	23·4 (4 8)	13·3 (3·6)

*Clinical left ventricular failure, ventricular fibrillation, ventricular tachycardia, atrial fibrillation, heart block, and pericarditis.

maining 93 patients, 73 completed the 12 week exercise course, eight defaulted on return to work, four defaulted at other times, and six were withdrawn for medical reasons (one reinfarct, one left ventricular failure, one increasing angina and three orthopaedic problems). Thus 73 completed the course and 81 continued to exercise at least until they returned to work.

Of the 101 control patients, one died and one refused follow up. By the end of the 12 weeks of the trial, 27 of these were taking unsupervised, apparently vigorous exercise at least twice a week. These exercises included bicycling, using a bicycle ergometer, press ups and sit ups, swimming, jogging, and weight training.

CHANGES IN OBSERVATIONS (TABLE 3)

There were no significant differences between the two groups for change in frequency of sexual intercourse (Mann-Whitney U, $p = 0{\cdot}40$), resting heart rate ($t = 0{\cdot}64$, df = 173, $p = 0{\cdot}52$), blood cholesterol ($t = 0{\cdot}69$, df = 161, $p = 0{\cdot}49$), or triglyceride concentration (Mann-Whitney U, $p = 0{\cdot}88$). The mean increase in weight of the treatment patients was significantly greater than in the control patients (difference = 1·2 kg) (95% CI for difference = 0·06 to 1·98; $t = 2{\cdot}09$, df = 191, $p = 0{\cdot}04$).

Angina pectoris was present at the first follow up in 21 patients in the treatment group and in 20 control patients. By the second follow up angina was present in 19 (−10%) of the treatment patients but in 32 (+60%) of the controls. The increase in the occurrence of angina in the control group was significant (difference in proportions = 0·12) (McNemar's $\chi^2 = 7{\cdot}56$, 95% CI = 0·04 to 0·20; df = 1, $p = 0{\cdot}01$).

The median energy level for the treatment group rose from 50% before the exercise course to 95% after the exercise course with a median rise of 41%. The median energy level for the controls rose from 50% to 90% with a median rise of 25%. The median energy level was significantly greater in the treatment group than in the controls (difference = 10·00%) (Mann-Whitney U 95% CI = 0·00 to 21·92; $p = 0{\cdot}03$).

Fifty five of the treatment group and 60 of the controls had been cigarette smokers before their infarcts. By the end of the period of observation, 43 (78%) of the smokers in the treatment group and 52 (87%) in the control group said that they no longer smoked.

Table 2 Comparability of electrocardiographic changes in the two groups

	Anterior	Inferior	Lateral	Q waves
Treatment group (99)	47	45	7	73
Control group (101)	47	50	4	73

Among patients in the treatment group, of the 42 smokers who finished the exercise course, six (14%) continued to smoke, while of the 13 smokers who failed to finish the course six (46%) continued to smoke (difference in proportions = 0·32) ($\chi^2 = 4{\cdot}19$, 95% CI = 0·08 to 0·66; df = 1, $p = 0{\cdot}04$).

CHANGES IN EXERCISE TEST RESULTS

In the treatment group, the mean predicted maximum oxygen uptake rose significantly from 22·16 to 27·32 ml/min/kg (paired $t = 9{\cdot}69$, df = 77, $p < 0{\cdot}001$). In the control group, the mean predicted maximum oxygen uptake also rose significantly from 23·36 to 26·16 ml/min/kg (paired $t = 5{\cdot}71$, df = 79, $p < 0{\cdot}001$). The mean difference in the increase of predicted maximum oxygen uptake was 2·35 ml/min/kg, which was significantly greater (95% CI for the difference = 0·92 to 3·78; $t = 3{\cdot}24$, df = 156, $p = 0{\cdot}001$) in the treatment group than in the control group.

In the treatment group the mean double product at peak exercise decreased significantly from 246 to 212 (paired $t = -8{\cdot}71$, df = 84, $p < 0{\cdot}001$). In the control group the mean double product decreased from 230 to 228 (paired $t = -0{\cdot}54$, df = 84, $p = 0{\cdot}59$). The decrease in the mean double product was significantly greater in the treatment group than in the control group, difference = −32·58 (95% CI = −42·19 to −22·97; $t = -6{\cdot}70$, df = 168, $p < 0{\cdot}001$).

Discussion

In the United Kingdom, coronary rehabilitation courses are available to few patients recovering from cardiac surgery or myocardial infarction. The number has grown considerably since the British Cardiac Society review of 1970,[15] but many existing courses were established or initiated by nurses and physiotherapists with little support, and sometimes opposition, from doctors.[16] Such courses may, therefore, be underused and their effectiveness is seldom measured. This trial attempted to assess the effects of a community based exercise programme for patients immediately after infarction; it showed that most patients can participate (85% of patients who lived within 25 miles of the sports centre took part). Nearly all the treatment group embarked upon the

Table 3 Changes in important observations of the two groups

	Median frequency of sexual intercourse per month (interquartile range)	*Mean resting heart rate (beats/min) (SD)*	*Mean cholesterol (mmol/l) (SD)*	*Median triglyceride (mmol/l) (interquartile range)*	*Mean weight (kg) (SD)*
Treatment group:					
Number	94	88	81	81	94
Before	2·0 (0·0, 4·0)	79·5 (13·5)	6·2 (1·3) (0·9, 1·8)	1·3	75·2 (11·4)
After	1·0 (0·0, 4·0)	76·5 (10·5)	6·3 (1·0)	1·4 (1·0, 1·9)	76·4 (10·9)
Difference (after − before)	0·0 (−1·0, 0·0)	−3·0 (11·7)	1·3 (10·6)	−0·2 (−0·3, 0·5)	1·2 (3·0)
Control group:					
Number	99	87	82	82	99
Before	2·0 (1·0, 6·0)	79·0 (12·0)	6·1 (1·1)	1·3 (0·9, 1·8)	76·9 (9·7)
After	1·0 (0·0, 4·0)	74·9 (12·4)	6·1 (1·0)	1·4 (1·0, 2·1)	77·1 (9·3)
Difference (after − before)	0·0 (−2·0, 0·0)	−4·1 (9·5)	0·2 (10·3)	0·2 (−0·4, 0·6)	0·2 (3·8)

exercise programme: 81% continued to exercise until they returned to work and 73% completed the course, despite the fact that Alton Sports Centre is 15 miles from the centre of population. This figure is similar to that of Carson *et al* who found that 70% of 151 exercising patients completed a hospital based exercise programme.[5] Higher compliance rates (85–100%) have been achieved in selected patients referred for exercise.[11,17–20] One problem in assessing the results of exercise training in randomised trials is the tendency for control patients to take up exercise—the so-called drop-ins.[21] In our case 27% of the controls were taking apparently vigorous exercise by the end of the trial, though this was probably much less intensive and effective than the supervised exercise in the treatment group.

As with most other controlled trials of exercise for coronary patients, there was no difference between the groups for blood pressure,[7,22,23] cigarette smoking,[5,7] blood cholesterol,[4,5,24] and time to return to work.[1,4,5] It was surprising that there was no difference between the groups for change in triglyceride concentrations, which are reduced for up to 48 hours by vigorous exercise.[25] We made no attempt to relate the time of blood sampling to a previous exercise session.

Unfortunately the exercise testing of patients could not be blind because HJNB performed all the tests and supervised all the exercise sessions. Heart rate measurements were taken from an electrocardiographic write-out and should not have been subject to bias. However, it is possible that peak systolic blood pressures, read from an analogue electronic sphygmomanometer, were subject to observer bias.

The improvement in physical fitness of the control patients as measured by the predicted maximum oxygen uptake, was expected. The recovery of the heart from the immediate effects of the infarct produces a spontaneous improvement over the first three months[26] associated with an increase in stroke volume.[22] The large number of drop-ins, perhaps a result of the Hawthorne effect,[27] probably had little effect on the increased fitness of the controls (see below). The greater improvement in fitness among the treatment group testified to the effectiveness of the exercise regimen, and was of a similar order to that achieved in hospital based rehabilitation programmes.[2,3,5–9] This increase in physical work capacity produced by a short course of physical training is caused by peripheral adaptations rather than improved cardiac function.[28–30] There is an alteration in the distribution of blood within the working muscles and an increase in their capacity to extract oxygen, associated with an increase in the number and size of mitochondria, mitochondrial enzyme content, and capacity to metabolise various energy substrates.[31,32] The result of these changes is an increase in the arteriovenous oxygen difference of the blood flow to and from the working muscles.[28,33–35] Any given exercise load requires less blood to fuel it, with a reduction of demand on the heart and a lower heart rate.[35,36]

The reduction of exercise induced heart rate and blood pressure produced by exercise training of cardiac patients is a very important effect, because the heart rate × systolic pressure product (the double product) is a direct reflection of myocardial workload and oxygen demand.[37–39] The double product at submaximal workloads does not decrease spontaneously after infarction because the fall in heart rate response is matched by an increase in blood pressure response.[40,41] Because the control patients in this study showed no change in double product at submaximal workload it is likely that their improved fitness was largely due to spontaneous cardiac recovery and that the unprompted exercising of the drop-ins was relatively ineffective. The appreciable fall (by 14%) in the submaximal double product among the treatment group was reflected in their reduction in clinical angina compared with the controls, an effect that has been demonstrated in other controlled trials.[2,3,42] However, in this trial the symptom of angina was determined from the patient's history given to a research assistant who also helped at exercise sessions. A standardised questionnaire was not used and the findings of this symptom, which showed a larger than expected difference between the two groups at the end of the course, may have been biased.

Nearly all reports on the results of coronary rehabilitation have emphasised the great improvement in well-being and in psychological health it engendered. Few, however, have quantified this improvement, and those who have measured the psychological impact of rehabilitation have shown either no change[43] or rather minor benefit.[44-47] This study, too, found that the great improvement in subjective well-being among the treatment patients was nearly matched by the controls, implying that the overall effect of the physical training on this factor was modest. However, the combination of increased attention received by the controls[48] and the effect of the initial exercise test[49,50] may have given them a psychological advantage not shared by untreated patients who were not involved in controlled trials.

Most coronary rehabilitation programmes are based in hospitals, a few use home exercise,[4,8] and some are based in the community.[2,51,52] There are no published trials that compare the effectiveness or cost-effectiveness of hospital and community based programmes,[53] but in terms of adherence and measureable outcome the findings of our study are similar to those reported from hospitals. There are definite advantages in using community sports centres[54]—not only do they have more space than most hospitals but they also have the appropriate equipment for circuit training and have staff experienced in using it. An added benefit of exercising in the community is that it encourages a return to normal. The patient going to the sports centre is having fun rather than treatment and this should encourage compliance and, in the long term, lead to a habit of regular exercise.

This study showed the feasibility, the safety, and the benefits of a community based exercise programme supervised by a general practitioner for patients recovering from acute myocardial infarction. Every district general hospital should be able to offer this treatment to patients after myocardial infarction and those after coronary bypass graft but most do not. The community programme is one of the ways in which the gaps in the present provision could be filled.

HJNB was in receipt of grants from the British Heart Foundation and Wessex Regional Health Authority without which this trial would not have been possible. We thank Mrs Sally Turner, Mrs Carolyn Pape, and Mr Allen Larvan for their hard work

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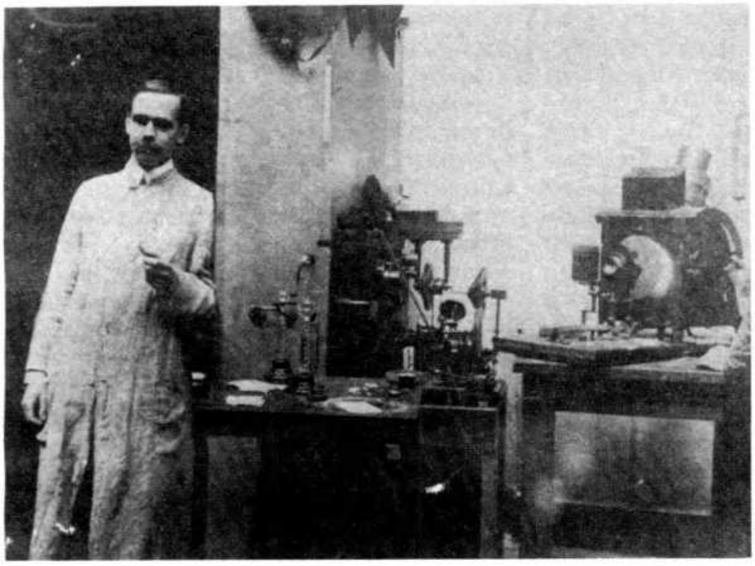
VIEWS FROM THE PAST *W A Jolly*



W A Jolly studied electrocardiography with Einthoven in 1908. On his return to Edinburgh in 1909 he and W T Ritchie recorded the first electrocardiogram showing atrial flutter. When he took up the chair of physiology in Cape Town in 1911 he brought with him the first electrocardiograph to be installed in South Africa; it is seen with him in this photograph. Source: Department of Physiology, University of Cape Town.

P C BELONJE, DENNIS M KRIKLER

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Changes in the electrocardiographic response to exercise in healthy women

Jaap W Deckers, Ruud V H Vinke, Jeroen R Vos, Maarten L Simoons

Abstract

Changes in the P wave, QRS complex, ST segment, and T wave during and after maximal exercise were quantitatively analysed in 116 healthy women with a mean age of 39. The corrected orthogonal Frank lead electrocardiogram was continuously recorded and computer processed during bicycle ergometry. With exercise, maximal spatial P wave vectors shifted downward. The Q wave amplitude became more negative and the R wave amplitude diminished considerably in leads X and Y: the S wave amplitude decreased only slightly in these leads. The QRS vectors shifted towards right and posteriorly during exertion and a further shift in the same direction was seen in the recovery period. The ST segment amplitude 60 ms after the J point decreased with exertion and became negative at heart rates above 140 beats per minute, in particular in lead Y. ST segment depression increased with age. The T wave amplitude decreased during exercise and increased sharply in the recovery period. Though mean R wave amplitude in leads X and Y became more negative with exercise, this response was unpredictable in individual women.

The exercise induced changes in QRS vectors in women resembled those described in men. Changes in the amplitude of the R wave should not be used for the diagnosis of coronary disease in women. ST segment depression was more pronounced in the inferiorly oriented lead Y than in lead X but it was unrelated to changes in the QRS vectors in these leads.

Exercise electrocardiography is an established method of predicting the presence of coronary disease in men but its value in women remains controversial.[1] Some studies have described considerable ST segment depression induced by exercise in symptom free women,[2-4] and in those with no angiographic evidence of coronary obstructions.[5-7] Others claim that the value of the exercise test in women is similar to that in men,[8-10] or that the high number of false positive tests in women can be attributed solely to their low prevalence of coronary disease.[11 12] One study suggested that the diagnostic value of the test in women could be improved if exercise induced QRS changes were taken into account.[13] Given these discrepancies, it is surprising that we know of no quantitative study of exercise induced electrocardiographic changes in women. Therefore, and in an attempt to elucidate possible sex differences in this response, we studied the electrocardiographic changes of the P wave, QRS complex, ST segment, and T wave during and after exercise in 116 female volunteers presumed to be free of cardiac disease.

Subjects and methods

One hundred and sixteen women performed a single exercise test. All were healthy volunteers without chest pain and without a history of cardiovascular disease. They had a normal electrocardiogram at rest, blood pressure of $\leqslant 165/95$ mm Hg, and a fasting serum cholesterol concentration $<6\cdot7$ mmol/l. Smoking history was not taken into account. They were not taking any medication. None had auscultatory findings suggestive of mitral valve prolapse or other forms of valve disease. Their mean (SD) age was 39 (10) years. Exercise tests were performed in the second half of 1978. After a mean follow up period of more than four years, none of them had died although seven could not be traced or had emigrated. The electrocardiograms of these seven women were reviewed separately but were retained in the study because their electrocardiographic amplitudes fell within the 5th and 95th percentile limits of the other women.

The women exercised seated on a calibrated bicycle ergometer. The workload was increased by 10 W per minute. The test was terminated when the subjects neared exhaustion. Cycling was continued at a low load for 4 minutes after peak exercise. The electrocardiogram was recorded through corrected orthogonal Frank leads with the chest electrodes at the level of the fifth intercostal space. The F electrode was placed on the sacrum and the H electrode on the neck. Careful attention was paid to proper preparation of the skin and fixation of the electrodes and wires. The electrocardiograms were computer processed as described in detail elsewhere.[14] In brief, the three orthogonal leads were sampled for 20 seconds with the subject at rest seated, every minute during exercise, and within six minutes of the end of exercise. The sampling frequency was 250 Hz. Beats showing abnormal QRS complexes or excessive baseline drift were rejected. An average representative complex was calculated from the remaining beats. Templates were used to define the onset

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and termination of QRS complexes.[15] The resting electrocardiogram of each subject was analysed with a general template. After visual inspection and validation of the reference points, patient specific templates were calculated and recorded.[14] The onset, peak, and end of the P and the T wave were also determined. For each lead, Q, R, and S waves were located. The baseline level was defined as the mean signal amplitude 5 to 3 samples (20 to 12 ms) before the QRS onset. All amplitudes were measured relative to this baseline. ST_{60} denotes the ST amplitude 60 ms after the J point. Orthogonal electrocardiographic amplitudes were converted to 12 lead electrocardiogram V5 amplitude according to Dower.[16]

STATISTICAL ANALYSIS

Statistical analysis, which included paired *t* tests to compare ST segment amplitudes and linear regression analysis and analysis of variance of electrocardiographic and clinical variables, was performed with the BMDP statistical program. Probability values of <0.05 were regarded as significant.

Results

The mean (SD) maximum workload achieved with exercise was 156 (32) W and the peak heart rate rose to 170 (16) beats/min. Systolic blood pressure rose from 137 (17) mm Hg at rest to 195 (18) mm Hg at peak exercise. Maximum heart rate and workload achieved decreased with age (table 1).

ELECTROCARDIOGRAPHIC CHANGES

P wave

The interval between the maximal spatial magnitude of the P wave and the onset of QRS complex decreased during exercise and lengthened again in the recovery period. Figure 1 shows the mean values of P amplitude in leads X, Y, and Z at increasing heart rates during exercise and at decreasing heart rates in the recovery period. P wave amplitude in leads X and Y (especially in lead Y) increased with exercise. The changes represent a gradual shift in the maximal P wave amplitude anteriorly, leftwards, and downwards. P wave amplitude at corresponding heart rates was higher in the recovery period than during exercise.

Table 1 Mean (SD) maximal heart rate, achieved workload, and ST segment amplitudes at peak exercise measured 80 ms after J in Frank leads X and Y in 116 healthy women in three age groups

	Age (yr)		
Variable	*<30 (n=25)*	*30–49 (n=76)*	*>50 (n=15)*
Peak heart rate (beats/min)	170 (21)	161 (23)	152 (25)
Workload (W)	172 (32)	154 (30)	134 (35)
ST_{80} lead X (μV)	30 (51)	18 (45)	22 (44)
ST_{80} lead Y (μV)	10 (50)	−9 (48)	−20 (44)

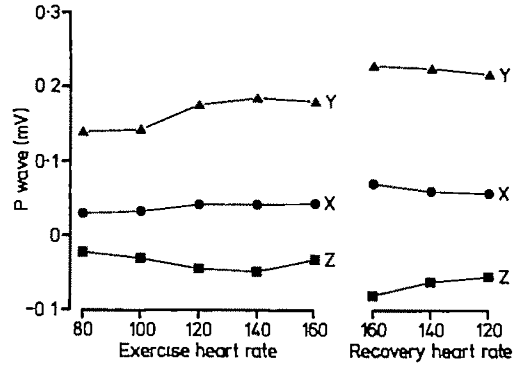

Figure 1 Changes in maximal P wave amplitude in Frank leads X, Y, and Z in women at heart rates of 80, 100, 120, 140, and 160 beats/min during exercise, and at heart rates of 160, 140, and 120 beats per minute during recovery.

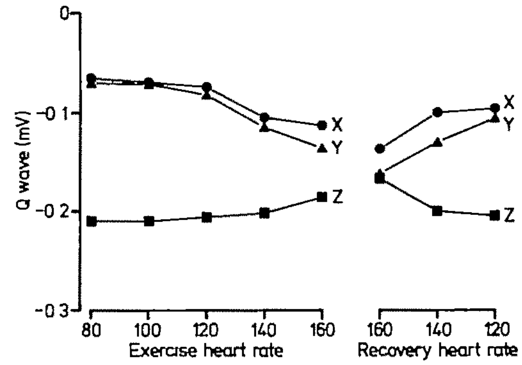

Figure 2 Changes in maximal Q wave amplitude in Frank leads X, Y, and Z in women at different heart rates during exercise and recovery.

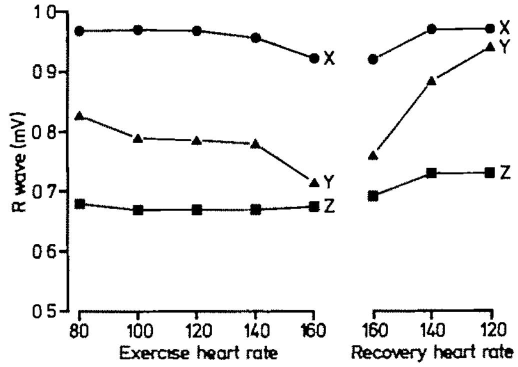

Figure 3 Changes in maximal R wave amplitude in Frank leads X, Y, and Z in women at different heart rates during exercise and recovery.

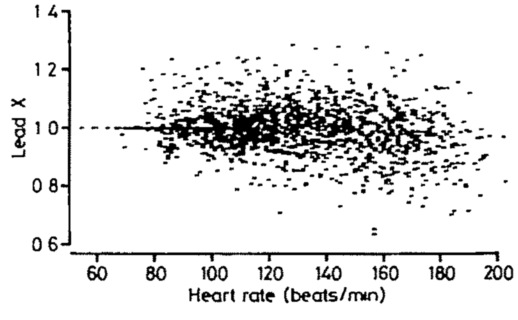

Figure 4 Individual changes in R wave amplitude in lead X during exercise in women. Measurements were made in relation to baseline R wave values.

Table 2 Changes in R wave amplitude during exercise in Frank leads X and Y in 116 healthy women

	Lead X	*Lead Y*
Increase >0·1 mV (%)	7 (6)	6 (5)
No change (%)	70 (60)	7 (6)
Decrease >0·1 mV (%)	31 (27)	65 (56)
Decrease >0·2 mV (%)	8 (7)	38 (33)

QRS COMPLEX

There was no significant change in QRS duration during exercise. The Q wave became more negative in leads X and Y at the end of exercise and less negative in lead Z (fig 2). The R wave decreased during exercise in leads X and Y but became slightly more positive at the end of the test in lead Z (fig 3).

Though the amplitude of the R wave decreased significantly during exercise, this response was extremely variable. Figure 4 shows the changes in R wave amplitude in lead X plotted against heart rate and the corresponding values at rest. In lead X at peak exercise the amplitude of the R wave decreased by at least 0·1 mV in 39 of the 116 women. Table 2 shows additional information on the R wave changes during exercise. In concordance with the R wave response, the amplitude of the S wave increased considerably at the end of exercise in leads X and Y, but remained unchanged in lead Z (fig 5). Taken as a whole the changes in the QRS complex correspond to a gradual shift of QRS vectors during exercise rightwards and posteriorly, with a further shift in the same direction in the recovery period.

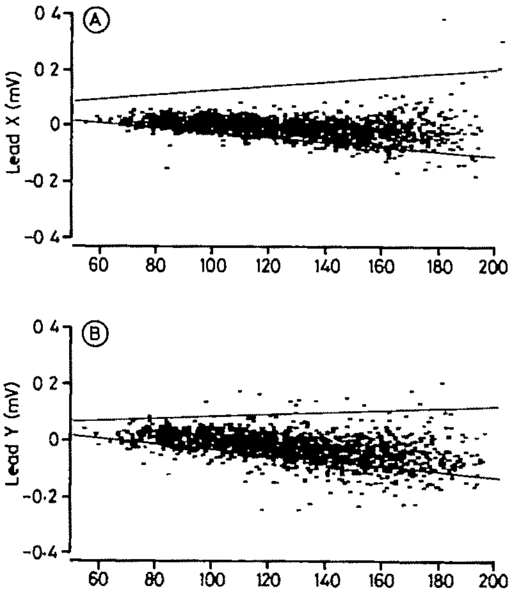

Figure 6 Individual changes in ST segment amplitude in Frank leads X (A) and (B) Y 60 ms after the J point in women during exercise. The 5 and 95 percentile limits for the same measurement in male volunteers are shown.[17]

ST segment

ST segment amplitudes in leads X and Y decreased with increases in heart rate; but significantly more so in the inferiorly oriented lead. Figures 6A and 6B show ST segment amplitude in leads X and Y plotted against heart rate. Many of the ST measurements were in the lower range or even outside the 5 and 95 percentile limits previously reported in male volunteers.[17] ST segment depression was significantly ($p < 0·001$) more pronounced in lead Y than in lead X at heart rate between 100 and 160 beats/min. For instance, in lead X at a heart rate of 140 beats/min mean (SD) ST_{60} was −0·015 (0·032) (ST_{80}, 0·019 (0·040)) mV. At the same heart rate in lead Y, ST_{60} was −0·037 (0·046) mV (ST_{80}, −0·021 (0·055) mV). ST_{60} in the computed lead V5 at a heart rate of 140 beats/min was also negative (−0·011) (ST_{80}, 0·028) mV. ST segment amplitudes in leads X and Y became less negative at very high heart rate levels. To test the hypothesis that the different ST segment response in leads X and Y was related to changes in, or absolute values of, R wave amplitude, ST segment amplitude changes were adjusted for R wave amplitude at rest and at peak exercise in the various leads. No relation, however, was found between these electrocardiographic variables. ST segment amplitude became more negative with increasing age (table 1), and was thus associated with changes in heart rate as well as with age. This was particularly true in lead Y at heart rates of $\leqslant 160$ beats per minute. Figure 7 shows ST segment changes during exercise in relation to the ST segment amplitudes in these leads at rest; this shows the different behaviour of the

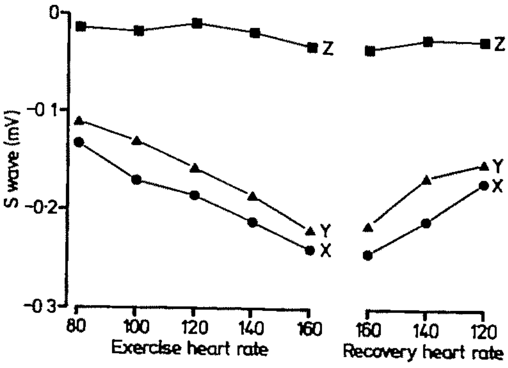

Figure 5 Changes in maximal S wave amplitudes in Frank leads X, Y, and Z in women at different heart rates during exercise and recovery.

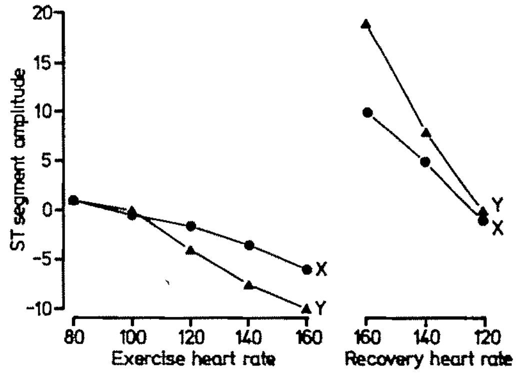

Figure 7 Changes in ST segment amplitude in Frank leads X and Y 60 ms after the J point at different heart rates during exercise and recovery in women. The measurement is given in relation to baseline ST segment amplitudes.

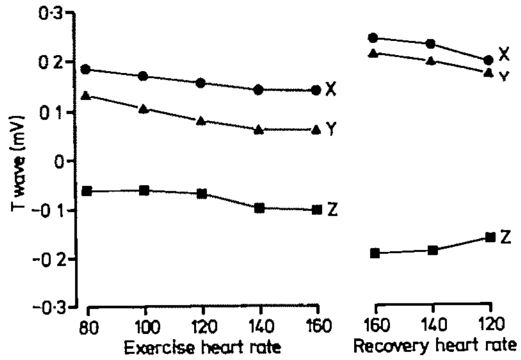

Figure 8 Changes in maximal T wave amplitudes in Frank leads X and Y in women at different heart rates during exercise and recovery.

ST segment response in lead X and Y during exercise in women.

T wave

During exercise the QT interval gradually shortened. T wave amplitude decreased early during exercise, but increased sharply in all leads immediately after the end of exertion (fig 8). There was a shift of the T wave rightwards and superiorly that was linearly dependent on heart rate during exercise.

Discussion

The continuing controversy about the clinical significance of electrocardiographic changes in women during exercise has limited the usefulness of the test.[18,19] Reference values for the exercise induced electrocardiographic changes and variations in this response have been accurately established in men,[20–22] but not in women.

Our study had limitations. We studied healthy women with a mean age of 39 years; the results may be different in older women with symptoms who are screened for coronary artery disease in various clinical or outpatient settings. Also the exercise tests were performed ten years ago; but we doubt that there were significant secular trends in the characteristics of healthy women during this time. The observed association between age and ST segment change should be considered in the light of the small number of elderly women in our study group. The study subjects did perform a maximal stress test—as indicated by the workload achieved, the peak heart rate, and systolic blood pressure.[3,23]

Our study showed that with exercise maximal P wave vectors shifted predominantly downwards, whereas maximal QRS vectors shifted to the right and posteriorly. The observed changes in P wave, QRS complex, and T wave in women resemble those described in men.[17,20,21]

Bonoris *et al* and Baron *et al* suggested that an increase in R wave amplitude during exercise was of diagnostic importance,[24,25] but the present results, indicating a highly unpredictable individual R wave response, do not support this. Others were also unable to confirm the diagnostic value of R wave amplitude changes.[26–28] Part of the reported differences between R wave changes in subjects with and without coronary disease may be the result of differences in peak heart rate during the test. For example, Ilsley *et al* found that women with coronary disease had lower peak heart rates than those without (107 beats/min *v* 130 beats/min).[13] In our study, mean R wave amplitude decreased during peak exercise in leads X and Y, but individual R wave changes were highly variable. In many tests R wave amplitude did not change or even increased either at the end of exercise or during lower levels of exercise. This phenomenon, also reported by others,[21] shows that R wave changes should not be used for the diagnosis of coronary disease in women. We performed a detailed analysis of the change in ST segment amplitude during exercise. ST segment amplitude in leads X and Y decreased significantly as heart rate increased: these changes which were augmented by age, were most noticeable in lead Y at heart rates of 120–160 beats/min. Our data indicate that in response to exercise S wave vectors behaved similarly in these leads, making it unlikely that the behaviour of the S wave was responsible for this finding. Like others,[29] we did not find a relation between the height of the R wave and subsequent ST segment depression in that lead.

Many reports have examined the diagnostic and prognostic value of exercise induced ST segment changes in women. In symptom free, healthy volunteers, ST segment depression of ⩾1 mm was reported in 2%[30] to 50% of middle aged women.[3,4] In follow up studies, exercise induced ST segment depression proved to be a poor predictor of future coronary events in symptom free women and in those with atypical chest complaints.[9,10,31] In a review by Guiteras *et al*,[32] the specificity of the exercise electrocardiogram in women with normal coronary arteries ranged from 63% to 92%.[11,33] Leading studies that compared ST segment changes in women with those in men always found that the specificity in men was slightly higher.[7,11,12] For example, in the large series reported by Weiner *et al*, the specificity of the electrocardiographic response to exercise in the total population was 74% in men compared with 64% in women.[12] However, in a paired subgroup matched for age and the presence and extent of coronary artery disease, no statistically significant differences were found between men and women in the percentages of false positive and false negative results. Although the present findings suggest that there is indeed a different ST segment response with higher heart rates in men and women, these conclusions have to be interpreted with some caution. The two studies were not performed at the same time in our institution and the mean age of the men was higher.[17] On the other hand, given the predominance of younger women in this study and the observation that ST segment depression increases with age, the present study may actually have underestimated the prevalence of ST segment depression in middle aged women. The conclusion that the prevalence of ST segment depression in women increases with age is supported by other reports.[2,3,30]

The present quantitative data indicate that ST segment depression is especially common in women at high heart rates in the inferiorly oriented lead Y. Sketch *et al* too reported that a higher ST segment depression was more common in leads II, III, and aVF in 46 women without significant coronary disease.[1] Guiteras *et al* too found that the specificity of the exercise induced ST segment depression in women was dependent on the electrocardiographic lead chosen, with lowest specificity in leads II, III, aVF, V5, and CM5.[32]

Mechanisms that may contribute to the changes in P waves, QRS complexes, and ST segment during exercise have been summarised elsewhere.[17 20] Changes in the position of electrodes relative to the heart, in the ionic balance, in haematocrit, and in intracardiac volume have all been implicated. There is no evidence that any one of these mechanisms acts differently in the two sexes and it seems unlikely that any of these factors can explain the different ST segment response to exercise in women. On the other hand, the observation that ST segment depression during exercise is more common in women cannot be explained solely by the lower incidence of coronary disease in women.[11] Other studies are warranted to identify this so-called non-Bayesian factor.

Our results indicate that in women exercise induced a downward shift of maximal P vectors and a shift rightwards and posteriorly of QRS vectors. This resembled the response in healthy men. Changes in R wave amplitude were unpredictable and should not be used for the diagnosis of coronary disease in women. ST segment depression increased with heart rate and with age. ST segment depression was more pronounced in lead Y than in lead X, though changes in S wave amplitude were similar in both leads.

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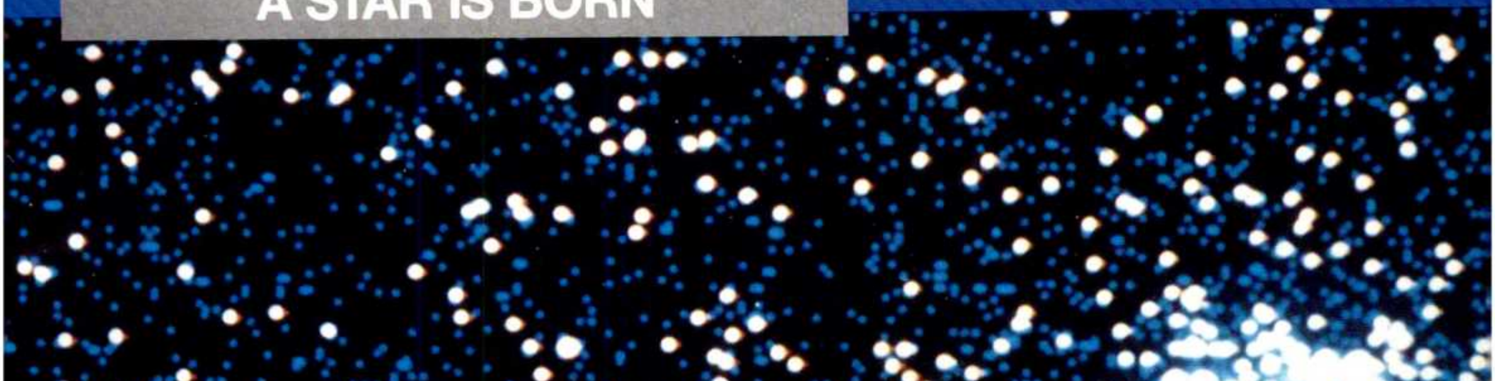

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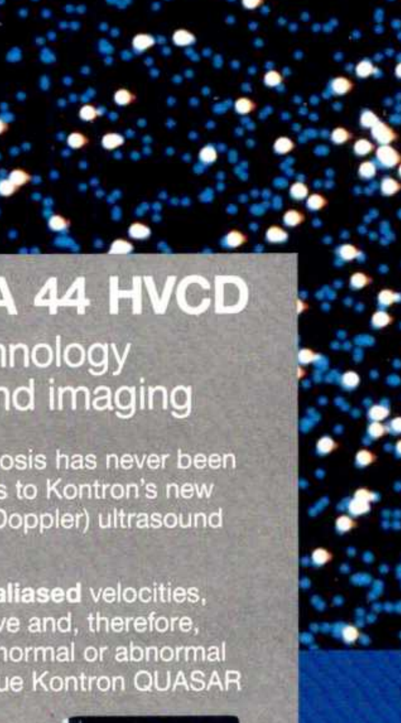

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Increase in native valve endocarditis caused by coagulase negative staphylococci: an Anglo-French clinical and microbiological study

Jérôme Etienne, Susannah J Eykyn

Abstract

Native valve endocarditis caused by coagulase negative staphylococci has become more common. A study of 35 cases showed that the infections were usually acquired in the community and occurred in men (mean age 51 years). A pre-existing cardiac abnormality (mitral leaflet prolapse in a third of patients) was detected in 26 (74%). The source of the organisms in the community acquired infections was assumed to be the skin, though lesions were seldom demonstrated; most hospital acquired infections resulted from intravenous devices. Community acquired organisms were usually sensitive to penicillin, whereas those acquired in hospital were often multiresistant. Most infections were caused by *Staphylococcus epidermidis*. The frequency of acute presentation (26%) and of major neurological abnormality (23%), together with the need for valve replacement (often emergency) (51%) and the mortality (36%) suggest that coagulase negative staphylococci can be virulent aggressive pathogens, mimicking *Staphylococcus aureus*.

It has long been recognised that coagulase negative staphylococci can cause infective endocarditis on native heart valves. In series reported before valve replacement surgery became available coagulase negative staphylococcal infection was responsible for about 1% of cases.[1 2] Some later series have reported a higher incidence,[3 4] but these have included both native and prosthetic infections and coagulase negative staphylococci are the commonest pathogens in prosthetic valve endocarditis. We recently noticed in our two hospitals a considerable increase in infective endocarditis of native valves caused by coagulase negative staphylococci. There were no cases in St Thomas's Hospital between 1968 (when detailed records began) and 1976, but between 1977 and 1989 there were 16 cases, accounting for 10·4% of the 154 cases of infective endocarditis of native valves seen during the period. In the Hôpital Louis Pradel, Lyon, no cases were detected between 1970 (when detailed records began) and 1975, but between 1976 and 1989 there were 19 cases, accounting for 4·4% of the 430 cases of native valve endocarditis seen. We present the clinical, microbiological, and epidemiological features of the infection in these 35 patients.

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Patients and methods

In both hospitals, the medical staff of the microbiology department, in close liaison with their clinical colleagues, keep detailed prospective records on every patient with infective endocarditis. These records together with hospital inpatient notes provided the data for this study.

The diagnosis of infective endocarditis was based on the isolation of the same coagulase negative staphylococcus from at least two sets of blood cultures and a compatible clinical syndrome (fever together with a new or changing cardiac murmur, embolic or cutaneous manifestations), or operative or necropsy evidence of endocarditis. In St Thomas's Hospital strains were sent to Dr R Marples of the Staphylococcus Reference Unit, Central Public Health Laboratory, Colindale, for identification and typing, though latterly they were also speciated at St Thomas's Hospital by the API STAPH (API System, Montalieu-Vereieu, France) and most recently ATB 32 STAPH (API System) systems. The French strains were identified by the same systems at the Centre National de Reference des Staphylocoques (Professor J Fleurette). Susceptibility to a range of anti-staphylococcal antibiotics was estimated by a diffusion method and results confirmed in many cases by estimation of the minimum inhibitory and bactericidal concentrations.

Results

Clinical and microbiological features and the treatment and outcome of the British and French cases seemed to be similar.

CLINICAL FEATURES

Twenty seven of the 35 patients with coagulase negative staphylococcal endocarditis on a native valve seen during the 14 year period were men (mean age 51 years (range 20–80 yr) and eight were women (mean age 52 years (range 21–76 yr)). None was a drug addict.

The length of symptoms varied: in 14 (41%) patients symptoms had been present for ⩾2 months (maximum 7 months), in eight (24%) for 2–8 weeks, and in nine (26%) for <2 weeks (in 6 of these nine cases they had been present for less than a week). Three patients presented with an acute cerebrovascular episode, and endocarditis was diagnosed in one when she was admitted to hospital for an elective valve replacement for calcific aortic stenosis. Fever was a constant finding, with weight loss and anorexia usual in the chronic cases. Cutaneous manifestations were detected in 11 (31%) patients (clubbing five, Osler's nodes four, splinter haemorrhages four) and splenomegaly in eight (23%). A major neurological abnormality was seen in eight (23%) patients; in seven this had precipitated referral to hospital and in the eighth hemiplegia developed after 4 days' treatment. These thromboembolic events included hemiplegia, dysphasia, and internuclear ophthalmoplegia. One patient presented with meningitis; his cerebrospinal fluid contained 1870 × 10^6 white blood cells per litre (95% polymorphonuclear cells) but was sterile on culture. He had a temporoparietal lesion, initially thought to be an abscess, but more probably of embolic origin. Peripheral emboli were detected in four patients.

Twenty six (74%) of the 35 patients had a pre-existing cardiac abnormality either congenital or acquired: mitral leaflet prolapse (eight) (one with Marfan's syndrome), bicuspid aortic valve (two), mitral leaflet prolapse plus bicuspid aortic valve with Marfan's syndrome (one), ventricular septal defect (one), rheumatic heart disease (two), murmurs of unknown aetiology (12). Twenty patients were known to have a predisposing cardiac abnormality, and four of them had experienced a previous episode of infective endocarditis with a different organism. In the other six patients the cardiac abnormality was detected during their admission with infective endocarditis. Infective endocarditis did not show a predelection for a particular valve. Haemodynamic failure was detected on admission in 19 (54%) patients.

Three patients complained of persistent backache; scanning and radiography showed evidence of vertebral osteomyelitis in the lumbar vertebrae in two patients and in both the lumbar and cervical vertebrae in the third. Though confirmatory biopsy specimens were not obtained, antibiotic treatment resulted in clinical and radiographic improvement.

LABORATORY INVESTIGATIONS

The mean haemoglobin at diagnosis was 113 g/l in men (range 78–155) and 104 g/l in women (range 89–132), the mean white blood cell count was 10·1 × 10^9 g/l (range 4·6–17 6), and the mean erythrocyte sedimentation rate for the 25 patients in whom it was measured was 63 mm/h (range 6–120). Haematuria was detected in eight (42%) of the 19 patients investigated by microscopy.

MICROBIOLOGICAL FINDINGS

In all 35 patients, at least two sets of blood cultures were positive for the same coagulase negative staphylococcus: in 25 (71%) every bottle yielded the pathogen, in seven of the other 10 patients at least 75% of bottles were positive, in two 50% were positive, and in one the coagulase negative staphylococcus was only recovered from three of 12 bottles.

In 32 (91%) patients the coagulase negative staphylococcus was *Staphylococcus epidermidis* (sensu stricto), in one patient accompanied by *S haemolyticus* in all bottles. Organisms from the other three patients were *S warneri*, *S hominis* (this could have been *S lugdunensis* because it was isolated in 1981, before *S lugdunensis* was described[5]), and a strain that defied satisfactory speciation.

Antibiotic susceptibility varied: 13 (36%) strains were sensitive to all anti-staphylococcal agents tested including penicillin, and eight (22%) were resistant to four or more antibiotics, always including penicillin, methicillin, and gentamicin. All isolates were sensitive to vancomycin.

EPIDEMIOLOGY OF THE INFECTION

Infections were classified as community acquired if the patient had no relevant recent history of hospital admission or treatment or as hospital acquired. In 23 (66%) the infection was community acquired: three patients had received dental treatment within the preceding 3 months without antibiotic prophylaxis (extractions in one, and other treatment not specified in two); a man with non-insulin dependent diabetes had cut his hand a week before malaise, fever, and chest pain developed. This lesion was healed on admission. One further patient, who had had a previous splenectomy, had an infected hand wound with lymphangitis six months before the onset of symptoms of endocarditis. No other predisposing factors could be identified, though one other patient had non-insulin dependent diabetes.

In the other 12 patients the infection was hospital acquired: in seven it resulted from an infected intravenous line, in one from the arteriovenous fistula used for haemodialysis, in one probably from a cardiac catheter two months earlier, and in one from urinary infection with the same strain after transurethral resection of prostate. In the other two patients whose infection was hospital acquired the source of the coagulase negative staphylococcus was less clear: one 21 year old woman with mitral leaflet prolapse and Marfan's syndrome became unwell within days of a forceps delivery; she had had an epidural and a single intravenous injection. The other patient became unwell after a cystoscopy and had had a peripheral cannula for intravenous access for 4 days. A constant feature of all these patients with hospital acquired infective endocarditis was previous antibiotic treatment. Whereas the coagulase negative staphylococci isolated from the community acquired infections were very sensitive to antibiotics, most strains from hospital acquired infections were multiresistant.

PROGRESS, TREATMENT, AND OUTCOME

Full details of follow up were available for all but two of the 35 patients; one of those lost to follow up refused the proposed valve replacement operation and discharged himself and the other had two recurrences of the infection, despite appropriate antibiotics, and returned to Iraq. Twelve (36%) of the remaining 33 patients died. Sixteen patients (46%) underwent valve(s) replacement during their admission with infective endocarditis; one required a second aortic valve replacement within 6 weeks of the first operation. Two patients required valve replacements 1 year and 3 years respectively after successful medical treatment of infective endocarditis. Six patients died after valve replacement as did six of those who did not have a valve replacement.

Both the antibiotic regimens used and the length of treatment varied. Patients nearly always received two antibiotics: usually a penicillin (occasionally a cephalosporin) plus an aminoglycoside; vancomycin, alone or in combination with various other agents was used for the multiresistant strains. The length of treatment in survivors varied from 2 weeks to 3 months. Pristinamycin, pefloxacin, and oxacillin were used in some of the French patients. No attempt was made to institute a standard regimen in either country. The choice of antibiotic was determined by the sensitivity of the organism and by the clinician in charge, advised by the microbiologist.

Discussion

This is the largest reported series of native valve endocarditis caused by coagulase negative staphylococci, an infection that has clearly become more common during the past decade. Sixty years ago, Thayer noted an incidence of "*Staphylococcus albus*" infective endocarditis of 1·96% in 306 cases observed over 40 years at Johns Hopkins Hospital,[1] but in a further 232 cases reported in the preceding 30 years he found only one other case, that reported by Lenhartz in 1901.[6] Thayer concluded that "endocarditis due to *Staphylococcus albus* is an occasional phenomenon". Twenty years later, Cates and Christie reported a 1% incidence of "*Staphylococcus albus*" in 408 culture positive cases of infective endocarditis.[2] In the 1950s the advent of mitral valvotomy and later of prosthetic valve replacement saw the emergence of coagulase negative staphylococci as major pathogens in post-cardiotomy endocarditis, particularly in individuals with prosthetic valves, and their role as pathogens in endocarditis of the native valve tended to be overlooked. Recent reports, including this study, suggest that the incidence of native valve endocarditis caused by coagulase negative staphylococci has increased.[7 8]

Coagulase negative staphylococci are normal inhabitants of the skin and mucous membranes and different species vary in their distribution throughout the body. It seems likely that coagulase negative staphylococcal endocarditis on native valves is largely an endogenous infection. There is good evidence that coagulase negative staphylococci elaborate some of the exoproteins produced by *S aureus*, some of which are recognised virulence factors.[9] These exoproteins may have a role in the pathogenicity of coagulase negative staphylococci. The epidemiology of coagulase negative staphylococcal endocarditis is more readily determined for infections acquired in hospital than those acquired in the community. Hospital acquired cases usually result from infection of intravascular catheters or devices. Nosocomial endocarditis is now as commonly caused by coagulase negative staphylococci as by *S aureus*.[10] In common with published reports, most of our infections were community acquired, often with no discernible source. Minor abrasions may well escape detection, and, as with *S aureus* infections, one has to conclude that the organism has come from the skin but its site of entry into the blood stream remains unknown. The relevance of dental treatment is difficult to assess, though a dental source for coagulase negative staphylococcal endocarditis has been reported[4 11] and coagulase negative staphylococci have been isolated from blood cultures taken after dental treatment.[12 13]

Although the clinical presentation was similar to that of infective endocarditis caused by "viridans" streptococci, certain features suggest that coagulase negative staphylococci are more aggressive pathogens: firstly, one quarter of the patients had had symptoms for <2 weeks, which is most unusual in "viridans" infection; secondly, 23% of patients had a major neurological abnormality, one with meningitis; and lastly, concomitant vertebral osteomyelitis was found in 9%. Tuazon and Miller reported two cases of osteomyelitis of the cervical spine (one with infective endocarditis, one without) among their 10 cases of serious infections with coagulase negative staphylococci,[14] and Wood *et al* reported a case of lumbar vertebral osteomyelitis and native valve infective endocarditis caused by *S warneri*.[15] The high mortality in our series and the need for valve replacement, in most cases during the initial period of treatment, suggest that coagulase negative staphylococci can be virulent destructive organisms resembling *S aureus* rather than "viridans" streptococci. Caputo *et al* reported a lower mortality (19%) in their 21 patients, but a similar proportion of valve replacement operations (43%).[7] The mortality rate for "viridans" infective endocarditis on native valves was 6% in Bayliss *et al*'s study in 1981–2,[3] 7% in cases seen at St Thomas's Hospital over the past 20 years, and 10% in Lyon since 1980. This compares with a mortality of 53% (26/48) in patients with *S aureus* on native valves (non-addicts) seen at St Thomas's Hospital over the same period and 39% (19/49) in Lyon.

Three quarters of our patients had a pre-existing cardiac abnormality, a similar figure to that reported by Caputo *et al* in their 21 cases of infective endocarditis caused by coagulase negative staphylococci.[7] The commonest congenital abnormality was mitral leaflet prolapse, detected in nine (26%) of our patients; this abnormality is being increasingly recognised as a precursor of endocarditis.[16] The association of coagulase negative staphylococcal endocarditis and mitral leaflet prolapse has been noted before.[8 17 18]

In common with other bacterial endocarditides the coagulase negative staphylococci were isolated from most blood cultures taken; and our rate of 71% of bottles resembles that reported by Caputo *et al* (67%).[7] In contrast, Quinn and Cox found that though blood cultures were uniformly positive from their patients with post-cardiotomy coagulase negative staphylococcal endocarditis, only one of nine of those with native valve infection showed this pattern.[4] More worrying was our patient from whom the infecting coagulase negative staphylococcus was only recovered from 3 of 12 bottles, and Quinn and Cox reported on a patient who received no antibiotic treatment for what was shown at necropsy to be infective endocarditis because the coagulase negative staphylococcus was only isolated from 2/9 blood cultures and was disregarded as a contaminant. Repeat isolation of the same coagulase negative staphylococcus from the blood, even if it is not consistent, should not lightly be dismissed as contamination.

Our series showed that *S epidermidis* (sensu stricto) was the commonest species causing infective endocarditis, but various other species can also cause the disease. Richardson *et al* found that *S epidermidis* accounted for a greater proportion of coagulase negative staphylococcal endocarditis on prosthetic valves than on native valves (85 *v* 56%).[19] Many reports, however, refer to *S epidermidis* without giving any information on speciation, and until recently it has been usual to label any coagulase negative staphylococcus as *S epidermidis*.

Antibiotic susceptibility was variable, but a major difference emerged between those strains acquired in the community and those acquired in hospital. Two thirds of strains acquired outside hospital were sensitive to all anti-staphylococcal agents including penicillin, and most of the others were resistant only to penicillin; whereas hospital strains were always resistant to penicillin and two thirds of them were multiresistant (including methicillin). In many reported cases of coagulase negative staphylococcal infection of a native valve the organisms were penicillin sensitive. This pattern of infection contrasts strongly with infective endocarditis caused by *S aureus* where most isolates, wherever acquired, are resistant only to penicillin.

We thank the clinicians in the Hópital Louis Pradel and St Thomas's Hospital for permission to study their patients, and Dr Yvonne Brun and Dr Michele Bes of Lyon and Dr R Marples of Colindale for identification and typing of the strains.

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Anomalous subaortic position of the brachiocephalic vein (innominate vein): an echocardiographic study

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Abstract

In 24 (0·98%) of 2457 patients with congenital heart disease the brachiocephalic vein was in an anomalous position below the aortic arch. This is a much higher proportion of such cases than reported so far. This high frequency may arise from differences in the study population and the method of diagnosis. This venous anomaly was more common in patients with tetralogy of Fallot or ventricular septal defect with pulmonary atresia. Patients with the venous anomaly were more likely to have a right aortic arch.

The anomalous course of the brachiocephalic vein from the neck to the junction of the superior vena cava was shown by cross sectional echocardiography. In doubtful cases, Doppler study usually clarified the anatomical arrangement.

The left innominate vein extends from the junction of the left internal jugular vein and the left subclavian vein to the superior vena cava. It runs above and in front of the aortic arch and in front of the left subclavian, left common carotid, and innominate arteries. In atrial situs inversus the arrangement of the systemic veins is usually the mirror image of this.

Rarely the left brachiocephalic vein takes an anomalous course below the aortic arch. This was first described by Kershner a hundred years ago.[1] Smallhorn *et al* described echocardiographic findings of this anomaly[2] and Gerlis and Ho recently reviewed a total of 25 patients including three of their own.[3] Though this anomaly is not clinically important, it may be confused with the pulmonary artery in cross sectional echocardiography especially in the patients with very hypoplastic or atretic central pulmonary arteries.

Gerlis and Ho thought that this venous anomaly was very rare—about one in 500 congenitally malformed hearts. But we found that this lesion is not rare in certain cardiac defects. We found 24 cases among 2457 echocardiograms of congenital heart disease in 21 months and we report the incidence and associated congenital heart diseases in this malformation.

Patients and methods

We reviewed echocardiograms obtained between January 1988 and September 1989 in the department of paediatrics, Seoul National University Children's Hospital to find out the total number of new patients with congenital heart disease, the types of cardiac defect, and the patients who had an anomalous brachiocephalic vein running below the aortic arch. If necessary, the diagnosis of the cardiac defects was updated after cardiac catheterisation or cardiac surgery.

The diagnosis of a subaortic brachiocephalic vein was mainly based on the cross sectional echocardiographic and Doppler findings. In the first few cases cardiac catheterisation confirmed the anomalous position of the brachiocephalic vein. Some cases had surgical confirmation too.

We used the χ^2 test or Fisher's exact test for statistical analysis and a p value $< 0·05$ was regarded as significant.

Results

Twenty four (0·98%) patients with an anomalous subaortic brachiocephalic vein were found among 2457 patients with congenital heart disease. Twenty three patients had a normally arranged atria and the left brachiocephalic veins were below the aortic arch. One patient had atrial inversion, a left sided superior vena cava, and a right brachiocephalic vein associated with a complex intracardiac defect. In this patient the right brachiocephalic vein was below the left aortic arch and intracardiac defects consisted of discordant atrioventricular connection with single atrioventricular valve, single aorta from right ventricle, and pulmonary atresia. Table 1 shows the frequency with which the venous anomaly was found in several cardiac malformations. It was very common in cases of tetralogy of Fallot and ventricular septal defect with pulmonary atresia. Table 2 summarises the clinical characteristics and the frequency of right aortic arch in the patients who had either tetralogy of Fallot or ventricular septal defect with

Table 1 Frequency of anomalous brachiocephalic vein in some cardiac malformations

Cardiac lesion	*No with cardiac defect*	*No with anomalous vein*	*Frequency (%)*
VSD	1042	1	0·01
TOF	177	10	5·7
VSD + PA	57	10	17·5
Others	1181	3*	
Total	2457	24	0·98

*Each patient had truncus arteriosus, complete transposition of the great arteries, and a complex anomaly with inverted atrial situs

PA, pulmonary atresia; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

Table 2 Clinical characteristics and laterality of aortic arch in patients with subaortic brachiocephalic vein

Cardiac defect (n)	*Age (mean) (range)*	*Sex ratio (M:F)*	*Proportion of right AA (%)*	*Proportion of right AA in those without venous anomaly (%)*
TOF (10)	1 yr 9 mnth (1 mnth–10 yr)	2·3:1	80	20·4
VSD + PA (10)	1 yr 9 mnth (3 mnth–10 yr)	2·3:1	50	21·3

AA, aortic arch. See footnote to table 1 for other abbreviations.

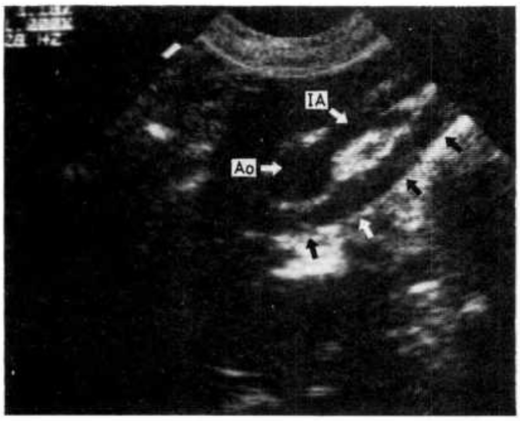

Figure 1 Frontal view from suprasternal notch showing the subaortic left brachiocephalic vein (arrows) running in front of the left subclavian artery and below the left innominate artery and aortic arch. Ao, aorta; IA, innominate artery.

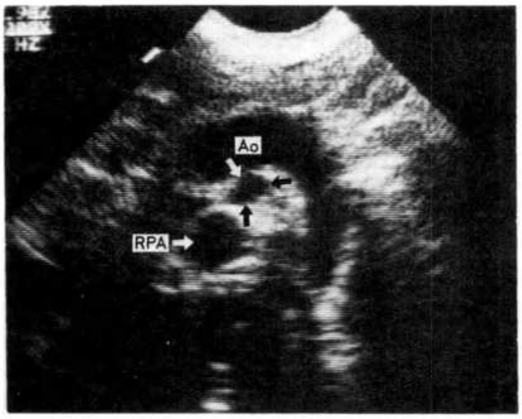

Figure 2 Suprasternal para-sagittal view shows two circular structures below the aortic arch. The upper circle (arrows) is the left brachiocephalic vein and the lower one is the right pulmonary artery (RPA).

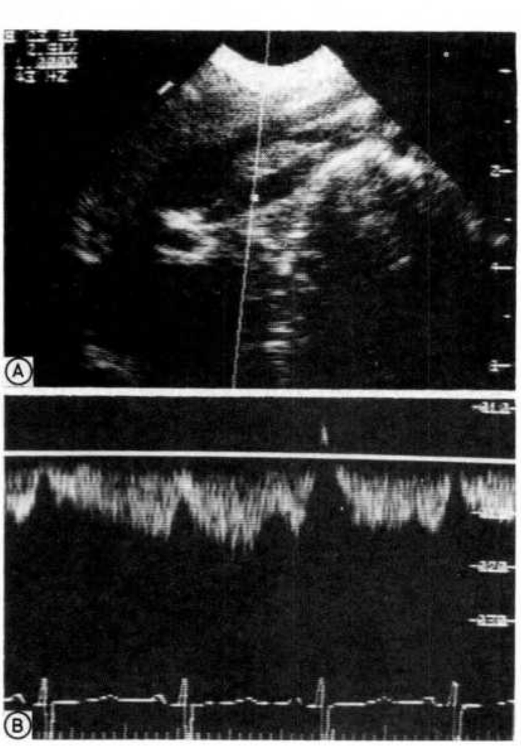

Figure 3 Doppler spectrum (B) recorded from the left brachiocephalic vein (A) and showing low velocity venous flow toward the heart.

associated pulmonary atresia and the brachiocephalic vein in an anomalous position. The table also shows how often a right aortic arch was diagnosed in patients with the same cardiac defects but without an anomalous brachiocephalic vein during the same period. A right aortic arch was significantly more common in patients with an anomalous vein than in those without ($p < 0·05$ in tetralogy of Fallot and $p < 0·05$ in ventricular septal defect with pulmonary atresia).

Five patients had a persistent ductus arteriosus. Three of them had a ventricular septal defect, pulmonary atresia, a right aortic arch, and a left ductus arteriosus arising from the left innominate artery. Another patient had tetralogy of Fallot, left aortic arch, and a left ductus arteriosus and the remaining patient had atrial situs inversus, a left aortic arch, right ductus arteriosus from the right innominate artery, and the intracardiac defects described earlier. The ductus arteriosus always passed in front of the anomalous brachiocephalic vein. Ten of the 19 patients without a persistent ductus arteriosus had an operation. But in the surgical descriptions of these operations there was no comment of the presence of a ligamentum arteriosum or its relation to the anomalous vein.

Cross sectional echocardiography in the suprasternal frontal plane showed the anomalous left brachiocephalic vein between the right pulmonary artery (below) and the aorta (above). This anomalous vein could usually be traced to the left side of the neck when the transducer is tilted leftwards and anteriorly. In patients with a right aortic arch and left innominate artery, the anomalous vein descended from the left side of the neck and crossed the left subclavian artery anteriorly, ran under the left innominate artery, and then joined the superior vena cava (fig 1). When the ductus arteriosus arose from the left innominate artery, slight tilting of the transducer showed the relation between the vein and the ductus. But in patients with a left aortic arch this vein ran in front of the left common carotid and left subclavian arteries so that it was very difficult to get a simultaneous demonstration of this vein and head and neck arteries.

The parasagittal view showed two circles below the aortic arch. The upper one is the anomalous vein and the lower one is the right pulmonary artery (fig 2). Doppler examination showed the typical venous flow signal toward the heart (fig 3).

Discussion

The anomalous subaortic course of the left brachiocephalic vein was first described about a hundred years ago.[1] Gerlis and Ho reviewed 25 cases, including three of their own patients.[3] They reported that all these patients had an anomalous left brachiocephalic vein. In our study we found one patient who had a right brachiocephalic vein below the left aortic arch with an inverted atrial arrangement. Gerlis and Ho estimated the incidence of this malformation to be about 0·2% in their necropsy series.

In our clinical study we found the anomaly in 0·98% of patients. This difference may be due to the difference in the study population and the method of diagnosis. The two echocardiographers in our laboratory are well aware of this anomalous position of the brachiocephalic vein and the echocardiographic findings when this lesion is present are so characteristic that they are unlikely to miss or overdiagnose this lesion. The lower incidence found in the necropsy series may have been lower because tetralogy of Fallot and ventricular septal defect with pulmonary atresia, both conditions in which the venous anomaly is common, do not have a high mortality rate. Therefore these two cardiac malformations were less common in the necropsy series. Furthermore this lesion might be missed during the routine examinations.

Because we do not know of another clinical study of the incidence of this venous anomaly it is impossible to tell whether there is a racial variation.

Smallhorn *et al* described the echocardiographic findings associated with anomalous brachiocephalic vein and cautioned that this lesion might be confused with the central pulmonary artery.[2] The echocardiographic findings in our cases are almost the same as those described by Smallhorn *et al*, and in addition, we found that this vein was usually traceable to the left side of the neck. If this vein is properly traced, it is not likely to be confused with other vessels, and in doubtful cases Doppler study usually clarifies the situation.

The most frequently associated cardiac defects were tetralogy of Fallot and ventricular septal defect with pulmonary atresia, both of which were present in 20 of the 24 cases with the venous anomaly. Another two patients had conotruncal anomalies—truncus arteriosus or transposition of the great arteries. There were 22 conotruncal anomalies in total. This association of anomalous subaortic brachiocephalic vein with the conotruncal anomalies seems to be highly significant. In addition, a right aortic arch was more common in patients with the venous anomaly than in those without. The embryological origins of the anomalous vein have been reviewed[3] but the relation between the abnormal position of the brachiocephalic vein, conotruncal cardiac anomalies, and the right aortic arch has yet to be established.

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Circadian variation of heart rate is affected by environment: a study of continuous electrocardiographic monitoring in members of a symphony orchestra

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Abstract

Twenty four hour ambulatory ST segment monitoring was performed on 48 members (43 players and five members of the management/technical team) of the British Broadcasting Corporation (BBC) symphony orchestra without a history of cardiac disease. This period included final rehearsals and live performances (for audience and radio) of music by Richard Strauss and Mozart at the Royal Festival Hall (n = 36) and Rachmaninov and Tchaikovsky at the Barbican Arts Centre (n = 21). During the period of monitoring one person (2%) had transient ST segment changes. Mean heart rates were significantly higher during the live performances than during the rehearsals. Mean heart rates during the live performance of Rachmaninov and Tchaikovsky were significantly higher than during Strauss and Mozart in those (n = 6) who were monitored on both occasions. Mean heart rates in the management and technical team were higher than those of the players. The recognised circadian pattern of heart rate, with a peak in the morning waking hours, was altered similarly during both concert days, with a primary peak occurring in the evening hours and a lesser peak in the morning for both musicians and management/technical staff.

This study showed that environmental factors are of primary importance in defining the circadian pattern of heart rate. This has important implications when identifying peak periods of cardiovascular stress and tailoring drug treatment for patients with angina pectoris.

The morning waking hours are the peak time for myocardial ischaemia,[1 2] acute myocardial infarction,[3 4] and sudden cardiac death.[5 6] Allied circadian patterns include morning peaks in heart rate,[7] blood pressure,[7] catecholamine and cortisol secretion,[8] coronary vasoconstriction,[9] platelet stickiness,[10] and a morning trough in fibrinolytic activity.[11 12] Studies have shown that β blockade, by blunting the increase in the determinants of myocardial oxygen consumption, significantly altered the circadian pattern of ischaemia,[1] myocardial infarction,[3 4] and sudden cardiac death.[13] The inference from these studies is that therapeutic protection should be maximal in the morning waking hours, and that at this time the determinants of myocardial oxygen consumption require suppression.

It is not clear whether the physiological pattern of heart rate alters appreciably in those who perform their primary activities in the evening or whether heart rate patterns are primarily related to the act of waking and are somewhat independent of the patterns of activity during daily life. To assess whether the circadian pattern of heart rate is significantly and reproducibly altered by work pattern we studied members of a symphony orchestra, who rose in the morning and were active during the day, before carrying out their major body of work in the evening.

We also assessed the cardiovascular responses of the orchestra during the rehearsals and the live performances and individual variations in response to different pieces of music. In view of the concern about "stress" in the players in an orchestra, we also investigated cardiovascular responses in members of the management and technical team for comparison.

Patients and methods

We studied 48 (36 men and 12 women aged 22–59 (mean 40)) members of the British Broadcasting Corporation Symphony Orchestra. All volunteered to undergo 24 hours of ambulatory ST segment monitoring on the day of a final rehearsal and live performance broadcast on radio 3. Five were members of the management and technical staff of the orchestra. Instruments played during the monitoring periods included the violin (10), viola (three), cello (five), double bass (four), flute (four), trumpet (two), trombone (two), clarinet (two), bassoon (two), horn (four), oboe (one), tuba (one), organ (one), and tympani (two).

Thirty six subjects (35 players, 1 management) underwent 24 hours of electrocardiographic monitoring. This period included a final rehearsal in the morning and a live performance of Richard Strauss (*Metamorphosen*, *Vier letze Lieder*, and *Die Frau ohne Schatten*) and Mozart (*Symphony No 40 in G minor (K550)*) in the evening, performed at the Royal Festival Hall. Monitoring started before the rehearsal and the monitors were removed the next morning. Because some of the players thought that playing Strauss and Mozart was not particularly stressful we also monitored 21 people (17 players, four management staff) for 24 hours during final rehearsal and a live performance of Rachmaninov (*Symphony No 2 in E minor*) and Tchaikovsky (*Concert Fantasy: Bluebird pas de deux* (Tchaikovsky/Stravinsky)) at the Barbican Arts Centre. Nine (all musicians) had previously been monitored at the Royal Festival Hall. Again monitoring was started before the rehearsal and the monitors were removed the next morning.

We used pregelled electrodes to record two bipolar leads (an anterior lead (CM5) and an inferior lead). The sites and method of application were described elsewhere.[14] Two channel recordings were taken on magnetic tape by an amplitude modulated dual channel recorder (Reynolds Tracker). All tapes were visually analysed at 60 times normal speed with a Reynolds Pathfinder 3 and printouts were at 25 m/s. Any rhythm disturbance or change in the ST segment was recorded. Significant ST segment depression was defined as planar or downsloping ST segment shift of >1 mm measured 0.08 s after the J point that persisted for >1 minute.

One of the 48 individuals who underwent continuous ambulatory electrocardiographic monitoring was excluded from subsequent analysis because he was taking medications likely to affect the heart rate pattern. No other subject was taking any such medications at the time of study. Tapes from a further two subjects in the second concert (both also underwent monitoring during the first concert) were unanalysable for technical reasons.

In addition to visual analysis, we obtained a computerised printout of the results of each tape, which included the maximum and minimum heart rate recorded every five minutes throughout the 24 hour period of monitoring (total of 576 heart rate measurements/person/24 h). A total of 32 832 heart rate measurements from the analysable tapes were then manually incorporated on to a computerised worksheet for further analysis.

STATISTICAL ANALYSIS

Maximum and minimum heart rates for each five minute recording were averaged for the musicians monitored on the day of the first concert, those monitored on the day of the second concert, and those monitored on both concert days. The mean maximum and minimum heart rates were plotted against time of day to show the circadian distributions. Mean hourly maximum and minimum heart rates were also plotted and two harmonic Fourier fits superimposed to elucidate the circadian patterns. We used mean hourly heart rates to compare the circadian patterns with those previously described in healthy volunteers.

We used the Wilcoxon signed rank sum test to compare the mean maximum heart rates achieved by the musicians during both live performances and rehearsals; the hourly mean maximum heart rates of the musicians monitored on the day of concert 1 with those monitored on the day of concert 2; the heart rates of the string section during concert 1 with those of the wind section in the same concert; and the hourly mean maximal heart rates of the management and technical staff with those of the musicians. We used the Wilcoxon matched pairs rank sum test to compare heart rates achieved during concert 1 with those in concert 2 in those who performed live on both monitoring days.

Results

Data on 42 players (six in both concerts) and five members of the management and technical staff were available for analysis.

Figure 1 shows the circadian pattern of heart rate (mean maximum and minimum) in all 42 musicians investigated. This shows a peak in the morning waking hours (the recognised time of maximal heart rate activity in healthy people), but a greater peak during the evening. To establish whether the pattern of heart rate responses differed on the two concert days we compared the mean maximal and minimal heart rates of those studied every five minutes throughout the days (fig 2). This shows that the circadian patterns of mean maximal and minimal heart rates were similar on both monitoring days with a peak in heart rate in the

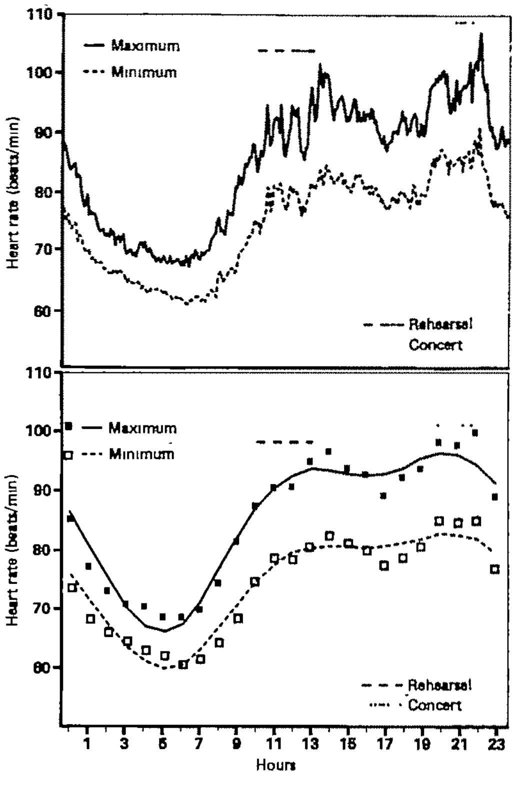

Figure 1 (Top) Circadian pattern of mean maximum and minimum heart rates measured every five minutes throughout the day in 42 players. (Bottom) Mean hourly maximum and minimum heart rates with bimodal fits superimposed. The approximate times of rehearsals and live performances are indicated.

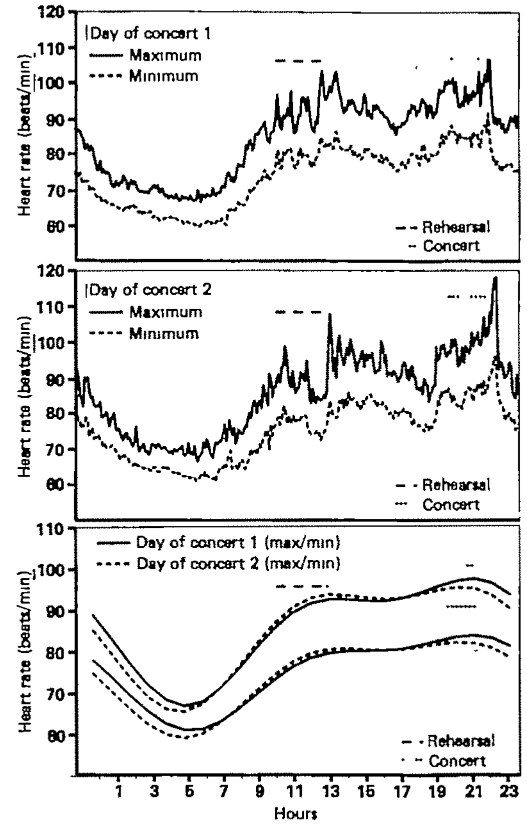

Figure 2 (Top) Circadian pattern of maximum and minimum heart rates measured every five minutes throughout the day in 34 players during 24 hours that included a concert (Strauss/Mozart). (Middle) Similar circadian pattern in 14 players throughout the day of the second concert (Rachmaninov/Tchaikovsky). (Bottom) Fourier fits of mean maximum and minimum hourly heart rates of the two concert days.

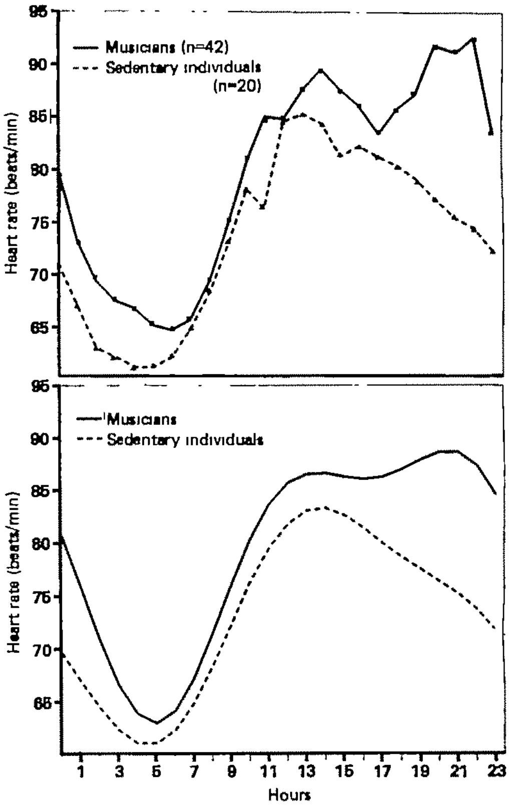

Figure 4 (Top) Comparison of the mean hourly heart rate changes in the 42 musicians during both monitoring days and the circadian pattern of mean hourly heart rates in 20 sedentary individuals.[15] (Bottom) Fourier fits of mean hourly heart rates in 42 musicians and 20 sedentary individuals.

evening hours. Except for two hours (13·00 h (97 beats/min concert 1 *v* 90 beats/min concert 2, $p < 0·05$) and 22·00 h (97 beats/min concert 1 *v* 106 beats/min concert 2, $p < 0·05$)) there were no significant differences in hourly mean maximal heart rates during the two concert days.

Mean maximum heart rates were significantly higher during the live performances than during the final rehearsals (concert 1, 97·7 *v* 91·3 beats/min, $p < 0·05$) (concert 2, 99·3 *v* 88·5 beats/min, $p < 0·05$). Though there was no significant difference in the mean maximum heart rates achieved by the musicians during the two live performances (97·7 *v* 99·3 beats/min), the six players (all wind and brass) who were monitored during both concerts had higher heart rates during Rachmaninov/Tchaikovsky (Rachmaninov/Tchaikovsky 95·7 *v* Strauss/Mozart 90·3 beats/min, $p < 0·05$). The mean maximal heart rate of the string section was significantly higher than that of the wind section during concert 1, which included *Metamorphosen* by Strauss for 23 solo strings (string section 100·2 *v* wind section 91·8 beats/min, $p < 0·05$).

We examined the mean hourly rate responses of the management and technical staff to establish whether the circadian pattern of heart rate responses differed in those who did not play an instrument. Figure 3 shows that the management and technical staff had a similar circadian pattern of heart rate to that of the musicians, with a primary peak in the evening hours. None the less, the management and technical staff had higher mean maximal heart rates throughout the day, and these differences were significant particularly in the periods leading up to the rehearsals and the live performances. Figure 4 shows the circadian pattern of heart rate in the 42 musicians monitored during the study compared with that of a group of 20 sedentary subjects described earlier.[15] This shows that the circadian pattern of heart rate in

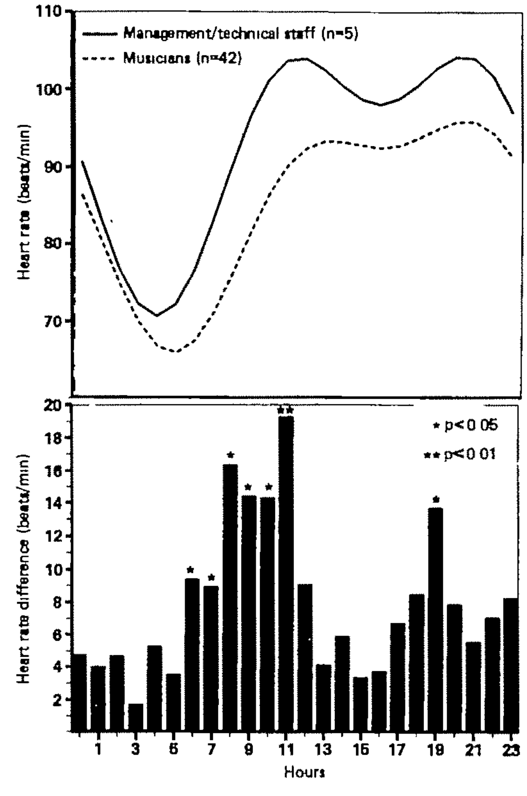

Figure 3 (Top) Circadian pattern of mean maximal heart rates in 42 musicians and 5 management/technical staff. (Bottom) Histogram showing the mean hourly differences in maximum heart rates between the management/technical staff and musicians.

the musicians was significantly altered at the times of the live performances.

Analysis of all tape results showed significant ST segment changes during the period of monitoring in one young subject (2%). No significant arrhythmias were recorded during the monitoring periods.

Discussion

For many years there has been a debate as to whether the onset of end points of cardiovascular disease is related to physical activity.[16 17] Muller *et al* in a review of circadian variation and triggers of onset of acute cardiovascular disease concluded that daily activities trigger the onset of most cases of myocardial infarction and sudden cardiac death.[18] There are distinctive circadian patterns of heart rate[7 15] and of different disease processes,[1-6] with a peak in the incidence of myocardial ischaemia,[1 2] acute myocardial infarction,[3 4] and sudden cardiac death[5 6] in the morning waking hours. Though it is impossible to assume a cause and effect relation between myocardial ischaemia and the development of both acute myocardial infarction and sudden cardiac death on the basis of these observations, it has been suggested that they may be interrelated.[19 20] The possible importance of changes in heart rate in the genesis of ischaemic episodes and various cardiovascular end points was suggested by the fact that whereas calcium antagonists with a coronary vasodilating capacity had no effect on the circadian pattern of ischaemia[1] or myocardial infarction,[4] β adrenergic blocking agents, which control heart rate and other determinants of myocardial oxygen consumption (thereby reducing myocardial oxygen demand), eliminated the distinctive morning peak of ischaemia,[1 21] acute myocardial infarction,[3 4] and sudden cardiac death.[13] Many studies reported that β blockade was effective in reducing the frequency of myocardial ischaemia,[21-25] though the underlying pathophysiological mechanisms of ischaemia were not clarified. One of the conclusions from the studies of circadian variation is that antianginal medications should be given to offer maximal protection during the morning waking hours, the apparent time of greatest cardiovascular threat.[1-6] Control of heart rate increase is of importance during this time.

To establish whether environmental factors do indeed significantly alter the recognised circadian pattern of heart rate, we studied a large group of patients who perform a normal day's work but whose major occupational efforts are in the evening. This distinguishes them from "shift workers" who maintain a normal sleep/wake/work pattern, despite having altered sleep/wake temporal patterns. We showed a considerable alteration in the circadian pattern of heart rate changes in such subjects, with the highest peak of activity in the evening hours, when most of their work was carried out, in addition to the early morning increase in heart rate as reported elsewhere.[7 15] The explanation for this evening increase in activity is not merely that of playing an instrument in front of an audience, because the same pattern was found in members of the management and technical team associated with the orchestra. In previous studies on the circadian patterns of ischaemia, infarction, and sudden cardiac death[1 3 5] a secondary evening peak in events was reported. This may have resulted simply from the fact that environmental circumstances lead to more cardiovascular stress in the evenings in some individuals, as shown in this study.

Northcote *et al* showed a circadian pattern of heart rate in individuals with a sedentary lifestyle that included some light activity.[15] This resembled the pattern reported by Millar-Craig *et al* in healthy individuals[7]—that is a peak in heart rate activity in the morning waking hours and a gradual decline during the later hours. The pattern of heart rate changes was different in orchestral musicians, who work in the evenings as well as during more conventional hours, and this pattern of change was reproducible on different occasions.

Though the people we studied had no cardiovascular symptoms; individuals with asymptomatic or symptomatic coronary artery disease are also likely to have similar alterations in their circadian pattern of heart rate changes in response to environmental stress and therefore it is important to tailor medications to offer maximal protection, not necessarily in the morning,[1] but at the times of identifiable cardiovascular stress during each patient's working day. We did not study the circadian patterns of blood pressure or catecholamine release in the present study; however, in earlier studies these variables peaked at the same time as heart rate changes,[7 8] and they probably reflect cardiovascular stress in much the same way as heart rate changes do.

The increased heart rates during the live performances indicate the pressure of performing for an audience—in the evening the relative rise in heart rate from resting values is probably considerably greater than the rise recorded in the morning. Like Haider and Groll-Knapp in their study of the Vienna Symphony Orchestra,[26] we too found that different pieces of music were associated with different levels of cardiovascular stress: though the overall changes in mean heart rate in both concerts were very similar, the heart rate change in the brass and wind players who were monitored during both concerts was greater during pieces by Rachmaninov and Tchaikovsky than during pieces by Strauss and Mozart.

The management and technical staff, who were responsible for ensuring the smooth running of the orchestra during performance days, had higher mean maximal heart rates than the players, mainly in the period leading up to the rehearsals and live performances. This accords with the theory that it is not the type of work that increases myocardial oxygen demand but the relative demands of getting the work done.

The lack of significant ST segment changes during ambulatory monitoring was somewhat surprising because a small but significant proportion of apparently healthy individuals had "ischaemic" ST segment changes during ambulatory monitoring.[27,28] This finding does, however, confirm that screening seldom detects abnormalities in apparently healthy individuals, even during periods of pronounced cardiovascular stress. It also reflects the unique benefits of ambulatory monitoring for continuous cardiovascular assessment of large numbers of individuals—even during live recordings on national radio. Under these circumstances we had to use soundless machinery. The heart rate findings show that in occupations such as symphony orchestra members there is a relatively high level of stress throughout the day, reflecting what is a long day's work, though the nocturnal heart rate pattern resembled that previously reported for similar groups of healthy volunteers.[7,15] To optimise treatment in patients with coronary artery disease the timing of occupational stress should be borne in mind.

We found that the circadian pattern of heart rate change was much influenced by environmental factors. The findings of previous studies, which identified the morning waking hours as the time of greatest cardiovascular danger, may in part have been the result of studying patients with normal working hours. The routine daily behavioural patterns of patients should be considered when tailoring treatment for optimal protection in patients with coronary artery disease. The pattern of heart rate (and probably blood pressure and catecholamine release) in those who work in the evening is likely to be different—with an increased risk of the end points of cardiovascular disease developing at this time. While it is not clear whether medical intervention to prevent possible triggers of end points of cardiovascular disease will reduce such episodes, it seems reasonable to assume that in patients with coronary artery disease optimal protection to minimise the physiological responses to stress will be beneficial. In the apparently healthy individuals that we studied, there was no evidence that any of the recorded cardiovascular responses were abnormal.

We would like to thank the Reynolds Medical Group for their cooperation in supplying the monitoring equipment for the periods of study, and the British Broadcasting Corporation Symphony Orchestra members for taking part in the study.

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Patients' observations of bioprosthetic valve failure: "My heart is honking, doctor"

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Abstract

Audible cardiac murmurs are uncommon and may indicate severe native valve dysfunction. In six patients with bioprosthetic mitral valves audible honking systolic murmurs suddenly developed. Doppler echocardiography showed characteristic striated regurgitant signals. At operation each prosthesis had torn cusps.

New audible murmurs and striated Doppler signals originating from mitral bioprosthetic valves are indicators of cusp tears. Recognition of this is important because early detection of prosthetic valve dysfunction may improve subsequent surgical outcome.

Audible honking murmurs have been heard throughout the cardiac cycle. Those in diastole have originated only from abnormal aortic valves. They have accompanied aortic cusp tears or leaflet prolapse arising either spontaneously[1] or from bacterial endocarditis[1] or syphilitic aortitis.[2 3]

Audible systolic honks have arisen from both the mitral and tricuspid valves. Mitral regurgitation in dilated cardiomyopathy,[4] mitral prolapse in adults[5] and in children,[6] and tricuspid prolapse[7] have all given honks audible to patients, sometimes in amusing or embarrassing circumstances.[6 8] Patients' descriptions of the murmurs differ but similes to animal noises are frequently used. We report on the menagerie of sounds that developed in six patients with mitral bioprosthetic valves and discuss their significance.

Case reports

CASE 1

A 57 year old woman had had a Carpentier–Edwards mitral valve prosthesis inserted 8 years before. While helping an elderly neighbour back to bed she was aware of the sudden development of a noise in her chest "like a goose honking". The noise was so loud she could not get back to sleep and she referred herself to us because she suspected something was amiss with her prosthetic heart valve.

On examination she had a grade 6/6 honking systolic murmur but no physical or radiological evidence of congestive heart failure. Echocardiography suggested a ruptured mitral prosthetic leaflet; mitral regurgitation was shown at angiography and she underwent an operation to replace the prosthetic mitral valve. Rupture of one of the prosthetic cusps was found at operation.

CASE 2

A 62 year old widower had been given a Hancock mitral valve replacement six years before. He awoke one morning and was aware of a noise within the house. He thought this was coming from his central heating and bled all his radiators but the noise persisted. His next thought was that a pigeon was trapped in a chimney but after examining all of his chimneys he could not find a bird. Then he realised with a start that the sound was coming from his own chest. He telephoned the hospital to report this new noise. Acute prosthetic mitral incompetence was confirmed by examination, echocardiography, and angiography. He had a successful repeat valve replacement and at operation the original prosthesis was found to have a ruptured cusp.

CASE 3

After lunch epigastric pain developed suddenly in a 73 year old woman in whom Carpentier–Edwards mitral and tricuspid valves had been implanted 11 years before. Simultaneously she became aware of a "squeaking" from her heart and then she became breathless. She was referred to hospital where a grade 6/6 honking systolic murmur was heard. Echocardiography detected leaflet prolapse in the mitral position and Doppler echocardiography showed a striated mitral regurgitant jet. Angiography confirmed severe mitral regurgitation and at operation the mitral prosthesis was found to have flail torn cusps.

CASE 4

A 56 year old woman had had an Ionescu–Shiley mitral valve implanted 6 years before. Her husband was woken in the night by a "squeaking" noise. He searched the bedroom for the source of the noise which he eventually discovered came from his wife's chest. He woke her and she confirmed his finding. The next day in the cardiology clinic a grade 6/6 honking systolic murmur was easily heard at the apex. Echocardiography showed a prolapsed prosthetic mitral cusp and Doppler ultrasound detected mitral prosthetic regurgitation with a striated Doppler signal (figure). She was referred directly for an operation at which one leaflet of the prosthesis was found to be torn at its base.

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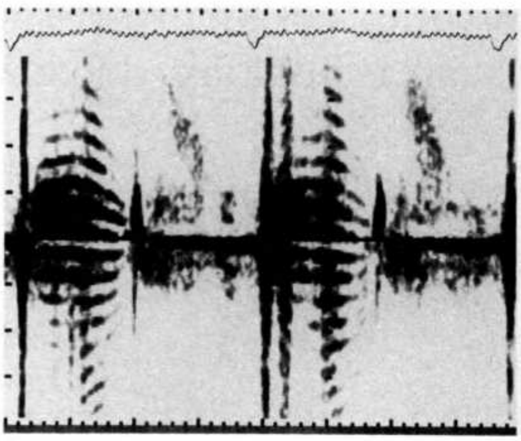

Pulsed wave Doppler echocardiogram from a patient with a ruptured cusp of a mitral bioprosthetic valve (case 4). The Doppler signal is striated suggesting harmonic summation of the ultrasound signal.

CASE 5

A 62 year old man had been given a Xenomedica mitral valve replacement six years before. His wife noted a grunting noise one morning at breakfast and they located it as coming from his chest. He quipped "if it's grunting it must be a pig's valve". He presented himself to our department. A 6/6 honking systolic murmur was heard and echocardiography and Doppler ultrasound showed features very similar to those in case 4. He was examined by coronary angiography which was normal and was referred for replacement of the prosthetic mitral valve.

CASE 6

An 83 year old man was kneeling by his bed at prayer one evening when he became aware that his utterances were accompanied by a cooing noise from his chest. That night he was troubled by breathlessness. Two days later he was admitted to hospital where a tear was found in his Hancock mitral prosthetic valve, which was implanted six years previously. Again Doppler echocardiography showed striated regurgitant signals.

Discussion

Loud honking systolic murmurs are typically associated with mitral valve prolapse[9] but they have also been noted in patients with regurgitant mitral porcine prostheses.[10 11] The murmur is probably caused by fluttering of cusp tissue. The striated Doppler echocardiographic signals are due to harmonic summation of the ultrasound beam reflected from the vibrating torn valve cusp. This Doppler echocardiographic appearance is characteristic of bioprosthetic cusp rupture.[12]

All the patients we describe presented because they heard a honking murmur. All were shown at operation to have rupture of the mitral bioprosthetic valve cusp. Acute prosthetic valve failure, which can usually be confirmed by Doppler echocardiography, should be suspected in all patients presenting with an audible honking systolic murmur. Only two of our patients presented with symptoms of breathlessness and in others the noise alone was the first indication of failure of the prosthetic valve. Surgical replacement of biological prosthetic valves carries a significant morbidity and mortality once heart failure has ensued. Such patients should be considered for urgent valve replacement before their condition deteriorates; this may occur rapidly. This is in contrast with honking murmurs associated with native valve prolapse which may be heard with all grades of severity of mitral reflux and do not imply an unstable condition.[9]

Failure of bioprosthetic heart valves is more common five or more years after implantation.[13 14] There is now a large cohort of patients with these prostheses implanted in the 1970s and early 1980s. Patients in whom a loud new murmur develops at a mitral prosthetic valve should be referred urgently to their cardiac centre.

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MEASUREMENT

A new method of haemodynamic assessment of mitral stenosis in atrial fibrillation: construction of a nomogram

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Abstract

Accurate haemodynamic assessment of mitral stenosis by hydraulic formulas requires measurement of the mean valve gradient and the cardiac output. The calculation is laborious, particularly in the presence of atrial fibrillation when averaged values obtained from multiple beat-to-beat determinations must be used. The relations between valve area, end diastolic gradient, and heart rate in 20 patients with mitral stenosis and atrial fibrillation were examined. In each patient the end diastolic pressure gradient for each cardiac cycle was related linearly to the RR interval of that cycle, and this relation was unchanged on exercise. The slope (S) and intercept (I) of this relation correlated with the degree of mitral stenosis as measured by the Gorlin valve area. The regression equations describing these relations were then used to construct a nomogram relating end diastolic pressure gradient to mitral valve area at different heart rates. When the nomogram was applied to catheterisation data from a further 30 patients the results correlated well with direct calculation of valve area by the Gorlin formula. The nomogram is simple to use, does not require measurement of cardiac output, and is independent of heart rate so that it is unnecessary for the patient to exercise during catheterisation.

Haemodynamic assessment of the severity of mitral stenosis from cardiac catheterisation data is time consuming, particularly for patients in atrial fibrillation. The most accurate methods use a hydraulic formula such as that of Gorlin and Gorlin,[1] which requires measurement of the cardiac output and the mean mitral valve gradient over 10 consecutive cardiac cycles (by planimetry or from digitised signals). In practice many cardiologists rely on the end diastolic gradient across the mitral valve.[2–5] Although it is recognised that this is highly dependent upon heart rate,[6–9] there are no published tables relating end diastolic gradient, heart rate, and the severity of stenosis. We therefore examined the relation between these variables in order to devise a method of estimating the severity of mitral stenosis and the mitral valve area from the simple measure of end diastolic gradient. A simple nomogram was constructed and the reliability of this approach was assessed in another group of patients.

Patients and methods

PATIENTS

Cardiac catheterisation data from an initial group of 20 patients were analysed in detail. All 20 were judged to have rheumatic valve disease on the basis of a past history of rheumatic fever and typical M mode echocardiographic features and all were in established atrial fibrillation.

To validate the nomogram constructed on the basis of the first 20 patients, we analysed cardiac catheterisation data in a further 30 patients. All had moderate or severe mitral stenosis; 25 were in established atrial fibrillation and five remained in sinus rhythm at the time of the investigation.

MEASUREMENTS

All patients were catheterised by the Sones technique, with an 8 French Sones catheter positioned in the body of the left ventricle and a 7 French Cournand catheter advanced to wedge in an upper lobe division of either the right or left pulmonary artery. The electrocardiogram, pulmonary artery wedge pressure, and the left ventricular pressure were recorded simultaneously at high paper speed of 100 mm/s and high sensitivity with careful calibration and balancing. In each patient 50 consecutive cardiac cycles were recorded at rest, while the patient was supine on the cardiac catheterisation table. In 10 patients who were able to perform supine straight leg raising exercises sufficient to increase mean heart rate by ≥ 20%, 50 consecutive cycles were also recorded immediately after this exercise. Cardiac output at rest was calculated by the indirect Fick method. The mitral valve area was calculated by the formula of Gorlin and Gorlin,[1] modified to take account of left ventricular pressure measured directly.[10]

The RR interval was measured from the peak of intrinsicoid QRS deflection to the peak of the intrinsicoid deflection of the next QRS complex; extrasystoles were included in

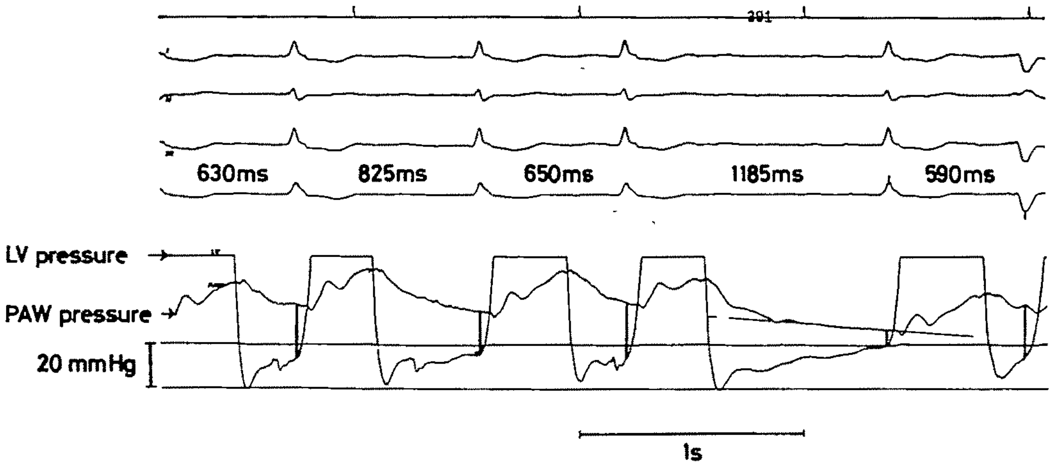

Figure 1 Measurement of mitral valve gradient at end diastole and RR interval for each cardiac cycle.

the analysis. The end diastolic gradient across the mitral valve was measured at the point of upward inflection in the left ventricular pressure trace or, if there was no well defined inflection, was taken at the peak of the intrinsicoid deflection of the QRS complex (see fig 1).

ANALYSIS

The relation between the end diastolic gradient across the mitral valve and RR interval in each subject was analysed by linear regression over the range of RR intervals at which the end diastolic gradient was greater than zero. The goodness of fit in each patient was judged by the Pearson product-moment correlation coefficient. When subjects were compared a normal distribution could not be assumed in view of the small numbers (20), and so we used the appropriate distribution-free statistic (Spearman rank correlation coefficient R).

Results

RELATION OF END DIASTOLIC GRADIENT TO RR INTERVAL

The range of RR intervals in each patient was (median) 470–1250 ms—the narrowest range being 550–1080 ms and the widest range 240–1875 ms. The relation between the end diastolic gradient across the mitral valve and RR interval was monotonic, with the end diastolic gradient decreasing as RR interval lengthened (Spearman $R > 0{\cdot}8$ in each of 20 patients) until a critical RR interval above which left ventricular and pulmonary artery wedges equilibrated and the end diastolic gradient was zero (fig 2). At RR intervals shorter than this critical RR interval the relation was approximately linear, and for each patient linear regression analysis was used to obtain the best fitting equation over this range. Goodness of fit judged by the Pearson correlation coefficient r over this range of RR was $> 0{\cdot}8$ in each individual patient.

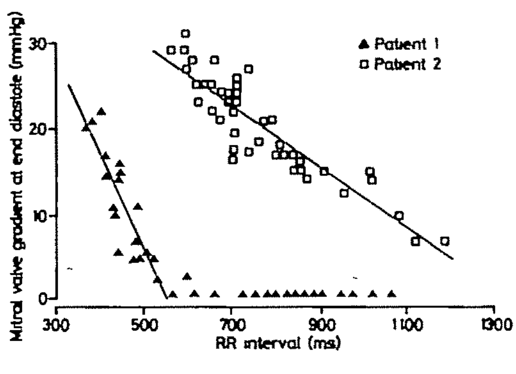

Figure 2 Examples of the relation between mitral valve gradient at end diastole and RR interval in two patients.

Supine exercise performed in 10 patients so as to increase mean heart rate by ≥ 20% over the resting state did not seem to influence the relation of end diastolic gradient to RR interval (fig 3). However, there was considerable scatter in the data points so that a given RR interval was associated with a range of end diastolic gradients. It is therefore possible that changes in the relation occur on exercise but are obscured by this variation.

CORRELATIONS WITH MITRAL VALVE AREA

There were significant correlations between the severity of mitral stenosis as measured by the mitral valve area calculated according to the Gorlin formula and the following variables:

(*a*) The slope of the relation of end diastolic mitral valve gradient to RR interval correlated with the Gorlin mitral valve area (MVA_G) for that patient (fig 4). The Spearman correlation coefficient was $R = +0{\cdot}88$ ($p < 0{\cdot}005$) and the linear regression equation was:

$$\text{slope} = 10{\cdot}4\,(MVA_G) - 1{\cdot}7.$$

(*b*) The intercept of the relation of end diastolic mitral valve gradient to RR interval correlated with the Gorlin mitral valve area for that patient (fig 5). The Spearman correlation coefficient was $R = -0{\cdot}90$ ($p < 0{\cdot}005$) and the linear regression equation was:

$$\text{intercept} = 1460 - 662\,(MVA_G).$$

Possible covariables in this analysis include age, height, and weight. However, the Gorlin mitral valve area was not found to be a function of age, height, or weight in this group of subjects. It is therefore unlikely that they confounded the analysis of MVA_G with respect to the slope or intercept.

NOMOGRAM

The above regression equations enabled the construction of a nomogram relating end diastolic mitral valve gradient to the Gorlin valve area at a range of different heart rates. Chosen values of Gorlin valve area (2·0, 1·5, 1·0, and 0·5 cm^2) were substituted in the equations, and the predicted lines relating end diastolic mitral valve gradient to RR interval were plotted in fig 5. Broken lines indicate the limits beyond which there are insufficient data to extrapolate these relations.

The nomogram permitted rapid estimation of valve area—for example the data in fig 1 show a cardiac cycle with RR interval 825 ms and an end diastolic gradient of 18 mm Hg. On the nomogram the estimated valve area lies between 0·5 cm^2 and 1·0 cm^2. Direct application of the Gorlin formula to the catheterisation data gave a valve area of 0·68 cm^2 in this patient. All the other cardiac cycles in this recording gave a similar estimate from the nomogram.

The nomogram was validated by analysis of cardiac catheterisation data for a further 30 patients with mitral stenosis (five in sinus rhythm and 25 in atrial fibrillation). The Gorlin valve area was first predicted from the nomogram by plotting the mitral valve gradient at end diastole against the RR interval for each of between two and five cardiac cycles. The valve area was then calculated directly from the indirect Fick cardiac output and 10 planimetered cardiac cycles by the Gorlin and Gorlin formula. In 25 out of 30 cases there was agreement, and in only one case was there a significant discrepancy (table).

Discussion

The dependence of the end diastolic mitral valve gradient on heart rate (and on RR interval) has long been appreciated.[6–9] It may be particularly difficult to interpret the end diastolic gradient at extremes of heart rate[11] and in patients in atrial fibrillation. Whereas corrections have been described for the effect of heart rate on the peak to peak aortic valve gradient,[12] none has been formulated for the mitral valve gradient. Accordingly, supine exercise during cardiac catheterisation has for many years been advocated as a means of identifying patients with important mitral stenosis who at rest have a normal or slow heart rate with only small to moderate transmitral gradients.[6 9] However, exercise during cardiac catheterisation is often hindered by patient discomfort, poor motivation, and the need to maintain sterility.[9] Increased ventilation by the patient may cause wide swings in intrathoracic pressure, confusing the interpretation of the pressure tracings.[9] In those patients unable to increase their heart rate sufficiently by exercise during catheterisation it has been suggested that atropine or dobutamine should be used.[13 14] The converse problem may arise in patients who are anxious or unwell at the time of catheterisation in whom it is not always possible or desirable to slow a fast heart rate. The effects of extreme heart rates on the assessment may unduly influence the choice between medical treatment and valve replacement or balloon dilatation if the severity of mitral stenosis is borderline.

The problem of differing heart rates in the

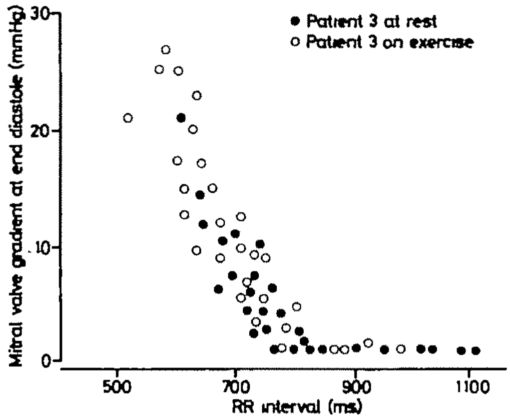

Figure 3 Relation between mitral valve gradient at end diastole and RR interval before and after exercise in one patient.

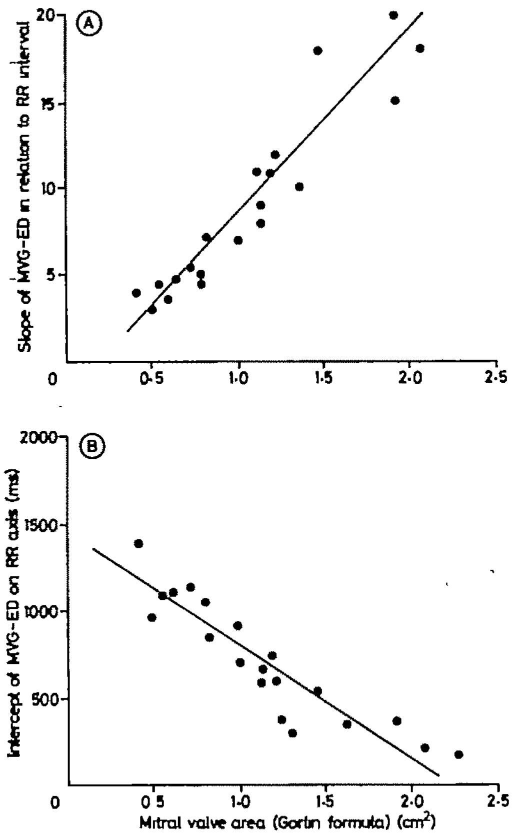

Figure 4 (A) Slope and (B) intercept of the mitral valve gradient at end diastole (MVG-ED) relation to RR interval and enclosed area plotted against the Gorlin mitral valve area.

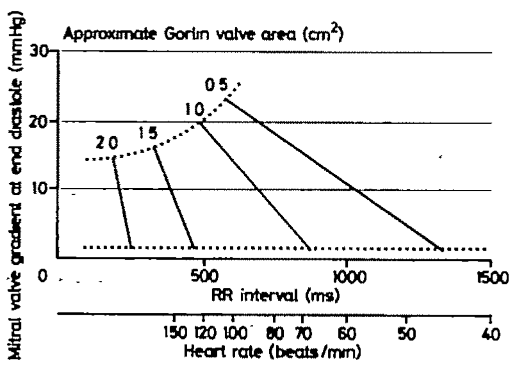

Figure 5 Nomogram to predict Gorlin valve area from mitral valve area at end diastole and RR interval or heart rate.

Mitral valve areas predicted by nomogram and directly calculated in 30 patients with mitral stenosis

Nomogram prediction (cm^2)	Gorlin mitral valve area (cm^2)				
	< 0·5	0·5–1·0	1·0–1·5	1·5–2·0	> 2·0
> 2·0					
1·5–2·0			1	3	
1·0–1·5		3	6		1
0·5–1·0		14			
< 0·5	2				

assessment of mitral stenosis can be partly avoided by applying hydraulic formulas to catheterisation data to calculate the effective area of the valve orifice. The best known and most widely used of the hydraulic formulas is that developed by Gorlin and Gorlin on the basis of Poiseuille's law and Torricelli's orifice equation.[1] This has the general form:

$$\text{valve area} = \frac{\text{mean flow rate through valve}}{\text{empirical constant} \times \sqrt{\text{mean pressure difference}}}$$

the empirical constant being different for mitral stenosis and for aortic stenosis.[1] Modifications to the original formula[15–18] and even new hydraulic formulas[19–21] have been proposed, but the Gorlin formula remains the most widely used.[4 5] Estimates of mitral valve area by this method correlate well with valve area determined at surgery,[1] although there may be a tendency systematically to underestimate valve area under conditions of very low cardiac output.[22 23] In the present study, resting cardiac output was $\geqslant$ 2·5 l/min in all cases (mean 3·4 l/min), so the Gorlin formula is likely to have provided an accurate estimate of valve area.

Non-invasive assessment of the severity of mitral stenosis by conventional or Doppler echocardiography or both is convenient and reliable.[24–26] However, echocardiography requires a skilled operator and clear recordings are not possible in up to 10% of patients.[27–29] Care is needed in interpretation because these methods may be inaccurate at fast heart rates and at high flows[30] and when the valve orifice is very small.[31] Mitral pressure half time in particular is influenced by several factors besides valve area.[21 32] Thus in patients undergoing cardiac catheterisation for another reason, such as coexisting coronary artery disease, the haemodynamic data obtained may be useful in assessing the severity of mitral stenosis.

Hydraulic formulas arguably provide the most accurate estimates of valve area,[1 5] but are tedious to use and require measurement of cardiac output. The labour can be reduced by digitisation of pressure signals to enable computed calculation, but such facilities are not widely available. The time taken for accurate planimetry led Potanin *et al* [33] to suggest superimposition of pressure tracings and visual comparison of areas as an alternative. However, like the nomogram of Negri *et al*[34] (based on a simplified hydraulic formula rather than the Gorlin formula) this approach still requires the cardiac output to be measured. A nomogram relating the end diastolic mitral valve gradient and heart rate to valve area might allow accurate assessment more conveniently than either Gorlin's original formula or Negri's nomogram.

Our data suggest that the relation between the end diastolic mitral valve gradient and RR interval is approximately linear. Regression analysis provides an equation for each patient that fits the data points well with correlation coefficient $r > 0{\cdot}8$, provided that care has been taken to obtain a technically satisfactory pulmonary wedge trace with little respiratory variation in the pressure. This linear relation contrasts with the time course of the left ventricular-pulmonary wedge pressure difference during diastole in each individual cardiac cycle, when the pressure difference seems to decline in an approximately exponential fashion. The explanation for this discrepancy is uncertain—it may depend on interactions between the length of preceding cardiac cycles and haemodynamic factors including left atrial filling[35] and the inotropic[36–38] and lusitropic[39–41] state of the left ventricle, which may be particularly complex in atrial fibrillation.[42] The simplicity of the linear relation between end diastolic gradient and RR interval is, however, an advantage in the construction of a nomogram (fig 5).

The nomogram is easy to use and a single data point may suffice. Any single cardiac cycle from the recording in fig 1 gave a point between the 0·5 cm^2 and 1·0 cm^2 lines of the nomogram when the Gorlin calculation gave a value of 0·68 cm^2 in that patient. The nomogram was validated by comparison with direct calculation of the valve area by the Gorlin formula in a separate group of 30 patients with mitral stenosis. There was agreement in 25/30 (83%) and disagreement in five. The largest difference was in a patient with a directly calculated valve area of 2·2 cm^2, in whom the nomogram predicted a valve area of between 1·0 and 1·5 cm^2. Even this difference, although undesirable, was unlikely to lead to a major change in the management of the individual patient.

The high level of agreement between nomogram estimates and direct Gorlin formula estimates of mitral valve area is perhaps surprising because cardiac output is required for calculation of the Gorlin valve but is not for the nomogram. Estimation of cardiac output is often inaccurate and this might be expected to produce discrepancies between the two methods. However, when the two methods were compared, the estimates of mitral valve area were divided into only five categories (corresponding to clinically very severe, severe, moderate, mild, and trivial mitral stenosis) (table). Thus even a 20–30% error in the estimation of cardiac output might not change the category of valve area into which the Gorlin formula estimate falls. Obviously in a simple analysis end diastolic gradient must depend upon cardiac output and flow rate across the valve as well as upon heart rate and mitral valve area. Furthermore, mitral valve area is, to a certain extent, influenced by flow rate. The apparent independence of the nomogram from the cardiac output may simply reflect a narrow range of cardiac outputs in the subjects in the study, or a systematic relation between valve area and resting cardiac output, or both.

There are several other sources of inaccuracy in the data from which the nomogram was derived that might reduce the accuracy of the nomogram. These are the use of fluid filled rather than transducer tipped catheters, the use of pulmonary capillary wedge pressure to reflect left atrial pressure, and the use of the indirect Fick method to measure cardiac output.

Another possible cause of error is mitral regurgitation, which leads to greater mean diastolic transmitral flow than would be calculated from the net forward cardiac output. This will lead to underestimation of mitral valve area by the Gorlin formula, on which this nomogram is based.[2] None of the subjects in the present study had mitral regurgitation in excess of angiographic grade 2: it is unlikely that the nomogram will be applicable in cases with severe mitral regurgitation. Subject to this restriction, the nomogram may be used in any patient in whom a significant end diastolic gradient has been recorded and can be related to the RR interval.

CONCLUSION

In mitral stenosis complicated by atrial fibrillation, the linear relation between RR interval and mitral valve gradient at end diastole permits the calculation of simple variables that correlate with mitral valve area calculated by the Gorlin formula. They can thus be used to assess the severity of mitral stenosis, and this is done most conveniently in the form of a nomogram. The nomogram correlates closely with the Gorlin hydraulic formula but is simpler to use and does not require cardiac output measurement. Furthermore, it is independent of heart rate and it is therefore unnecessary for the patient to exercise during cardiac catheterisation.

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CASE REPORTS

Acute pulmonary oedema on the Ruwenzori mountain range

Robert Naeije, Christian Mélot

Abstract
A 40 year old man had an episode of severe pulmonary oedema at 4000–5000 m during the ascent of the Margherita peak (5109 m) of Mount Stanley on the Ruwenzori. He had taken acetazolamide and high dose dexamethasone to treat symptoms of acute mountain sickness. Six years before he had been studied by right heart catheterisation as a healthy volunteer during hypoxic breathing at sea level. His pulmonary vascular reactivity had been within the normal range for 32 healthy subjects.

This man had high altitude pulmonary oedema despite currently recommended treatments for acute mountain sickness and normal pulmonary vascular reactivity to hypoxia at sea level.

High altitude pulmonary oedema is an uncommon but dangerous complication of acute mountain sickness that occurs in individuals rapidly ascending to >3000 m. High altitude pulmonary oedema is believed to be caused by excessive and uneven pulmonary vasoconstriction in response to hypoxia.[1] Whether susceptibility to high altitude pulmonary oedema can be reliably detected by testing pulmonary vascular reactivity to hypoxia at lower altitudes remains uncertain.[1-3]

A low rate of ascent and limited exertion usually prevent the development of acute mountain sickness and its complications. This is not always practical, especially during mountain rescues and military activities, nor is it an acceptable strategy when recreation time is limited. Many mountaineers attempt prophylaxis with pharmacological agents. Only acetazolamide and dexamethasone are known to be effective.[4]

We report a man with normal hypoxic pulmonary vasoconstriction at sea level in whom severe high altitude pulmonary oedema developed despite treatment with acetazolamide and dexamethasone.

Case report

This healthy 40 year old man flew from Brussels (sea level) to Kigali (Rwanda) (1500 m). He was susceptible to acute mountain sickness above 3500 m, but he had completed several difficult climbs in the European Alps. The day after his arrival he crossed into Zaire and drove 350 km in two days on a dust track to Mutuanga (about 1000 m), near the Ruwenzori range. For four days he marched through dense and boggy forest and over the muddy peat hags leading to the Margherita peak (5109 m) on Mount Stanley. With a party of two climbers and 10 porters, he carried a heavy pack up to the Kalonge hut (2138 m) on the first day of the march, to the Mahangu hut (3310 m), on the second, and to the Kiondo hut (4100 m) on the third. The next day he walked down to the Green Lake (3900 m) and up again to the Gray Lake (4200 m), at the edge of the West Stanley Glacier where the party set up a base camp. Since his arrival in Kigali he had been taking longacting acetazolamide (500 mg per day). On the third day of the march, he had a headache, lost his appetite, and slept poorly.

Seven days after his arrival in Africa he rested but was sick and drowsy with a headache, and ate little. He started to take dexamethasone (initial dose 8 mg then 4 mg every 6 hours). Next morning, after he had taken a total dose of 20 mg of dexamethasone, he was much improved though still anorectic. Soon after starting to lead the ice climb to the main summit he became very short of breath and coughed up blood tinged sputum. Close to the summit (5000 m) intense lassitude, dyspnoea, and a thick mist forced him to descend. Back at the base camp in the evening he was exhausted, very short of breath at the slightest effort, had an audible gurgling in his chest, blood stained sputum, and was suffocating in the supine position. He then realised he had high altitude pulmonary oedema and decided to try to get to a lower altitude while he was able to walk. Together with a companion and a porter, he reached Mutuanga the next day in the evening. For 48 hours he remained orthopnoeic and dyspnoeic on exertion or when drinking a beer. A physical examination performed by a local physician disclosed crepitant inspiratory rales over the lower half of both lungs that progressively cleared in 48 hours. The nearest *x* ray facility was two days drive away. Back in Brussels, physical examination, standard blood tests, electrocardiogram, chest *x* ray, and echocardiographic examination were normal.

Six years before he had been a healthy

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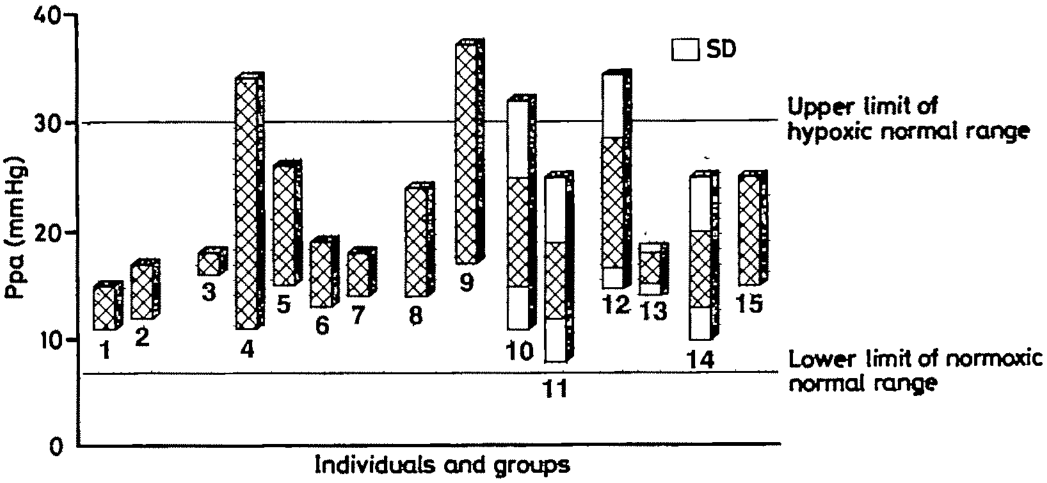

Hypoxic pulmonary pressor responses at sea level, expressed as absolute increases in mean pulmonary arterial pressure (Ppa), induced by an acute decrease in the fraction of inspired O_2 *(*FIO_2*) from 0·21 to 0·1–0 15 (hatched columns). Limits of normal (mean ± 2 SD) in 32 healthy volunteers reported by Naeije et al*[2] *(column 14) are represented by the stippled area. Columns 1 and 2 show a subject before and after high altitude pulmonary oedema*[2]*; columns 3 to 7 are five individuals with previous high altitude pulmonary oedema reported by Hultgren et al*[10]*; column 8 is an individual with previous high altitude pulmonary oedema reported by Peñazola and Sime*[6]*; column 9 is an individual who went above 5000 m without high altitude pulmonary oedema developing*[2]*; columns 10 and 11 show the mean (± SD) values for 44 subjects with previous high altitude pulmonary oedema and 51 controls respectively reported by Viswanathan et al*[11]*; columns 12 and 13 show the mean (± SD) values for five individuals with previous high altitude pulmonary oedema and five controls respectively reported by Kawashima et al*[12]*; and column 15 is the present case with previous high altitude pulmonary oedema. It is apparent that most individuals with previous high altitude pulmonary oedema have a normal pulmonary vascular reactivity to hypoxia at sea level.*

volunteer in pulmonary haemodynamic studies in our laboratory. A detailed description of the methods used was reported elsewhere.[5] When he was breathing room air, arterial Po_2 (Pao_2) was 12·8 kPa, $Paco_2$ 5·3 kPa, arterial pH 7·42, cardiac output (Q) 6·43 l/min, mean pulmonary arterial pressure (Ppa) 15 mm Hg, and mean pulmonary capillary wedge pressure (Ppw) 11 mm Hg. After 10 minutes of hypoxic breathing (12·5% oxygen balance nitrogen) Pao_2 was 4·8 kPa, $Paco_2$ 4·8 kPa, arterial pH 7·46, Q 8·4 l/min, Ppa 25 mm Hg, and Ppw 12 mm Hg. These values were within a normal range (mean ± 2 SD) for 32 healthy young adult volunteers (figure). For comparison, the figure includes normobaric hypoxic and normoxic Ppa measurements in adults with previous high altitude pulmonary oedema and in a man who on several occasions had walked at 5000–5500 m in Nepal without being ill. Most of the subjects with previous high altitude pulmonary oedema had a normal hypoxic pressor response.

Discussion

The Ruwenzori is a mountain range about 30 km north of the equator on the Uganda/Zaire border between lakes Mobutu (former Albert) and Amin (former Edward) in the great Western Rift Valley. These legendary mountains of the moon were known to Herodotus in 450 BC when he claimed them to be the source of the Nile. For centuries they were forgotten until Sir Henry Stanley explored them in 1876. The local people call them "the rainmaker" because they are mist shrouded and rarely visible. In the centre of the Ruwenzori range are six major massifs carrying permanent snow and glaciers, including the Margherita peak of Mount Stanley (5109 m) the third highest peak in Africa. The slopes leading to the main climbing routes of the Ruwenzori are steep, with at least 1000 m between the huts or shelters. The trails are too steep and rough for stretchers; plane or helicopter transportation is not organised; and medical facilities are remote (at least two days of driving on rough dust tracks in good weather).

These were the conditions in which this experienced mountaineer developed a lasting acute mountain sickness that was eventually complicated by coughing, haemoptysis, exertional dyspnoea, orthopnoea, and audible pulmonary rales, all features strongly suggestive of an episode of severe high altitude pulmonary oedema. Because prophylaxis with acetazolamide and dexamethasone probably lessened his non-respiratory symptoms he may have delayed his decision to descend. His pulmonary vascular reactivity to hypoxia was normal when it was tested at sea level.

In established high altitude pulmonary oedema, mean pulmonary arterial pressure is considerably raised in the face of normal pulmonary capillary wedge pressure or left atrial pressures.[6-8] Recent bronchopulmonary lavage studies in patients with high altitude pulmonary oedema showed a considerable increase in proteins of high molecular weight, but without the intense neutrophil accumulation that is typical of other forms of acute lung injury.[9] These data together with results of necropsy clearly indicate that in high altitude pulmonary oedema there is a high permeability lung oedema, for which the most likely explanation is a transient increase in shear forces caused by a sudden increase in mean pulmonary arterial pressure.[1] The finding of a normal acute hypoxic pulmonary pressor response in some children[3] and in many adults[2,6,10–12] at a lower altitude after an episode of high altitude pulmonary oedema does not exclude intense and possibly uneven pulmonary vasoconstriction as a contributing mechanism.[1] Other factors such as reduced atmospheric pressure, cold, exercise, or some other yet undetermined factor enhance the vasoconstricting effects of hypoxia in some individuals.[10,12] Even if a reliable non-invasive measurement of mean pulmonary arterial pressure were available, its use together with normobaric hypoxic testing would be unlikely to identify individuals who are susceptible to high altitude pulmonary oedema.

A stop of 2–5 days at an intermediate altitude (2000–3000 m) before climbers attempt the summit ("staging") and an ascent of less than 300 m per day above 3000 m are the conventional measures for avoiding mountain sickness.[1,4] But such advice conflicts with the desire of many travellers to arrive at their destination quickly or is impractical on mountains such as the Ruwenzori because of their height and the altitude differences between shelters. Prophylaxis with acetazolamide, an inhibitor of carbonic anhydrase, reduced the frequency of acute mountain sickness by 30%–50%.[1,4] Dexamethasone, an effective treatment of vasogenic brain oedema, has been recently evaluated because brain oedema may contribute to acute mountain sickness. At high doses this potent synthetic glucocorticoid was at least as effective a prophylactic treatment as acetazolamide.[4,13] Anecdotal reports recently suggested that dexamethasone might even be effective in the treatment of severe acute mountain sickness.[4] There are no data on the effects of combined acetazolamide and dexamethasone.[4] In our patient the addition of dexamethasone to acetazolamide resulted in such a subjective improvement that he undertook an ice climb, but symptoms of a life threatening pulmonary oedema then developed. Levine *et al* showed that dexamethasone improved the symptoms of acute mountain sickness in six individuals exposed to a simulated altitude of 3700 m in a hypobaric chamber but did not prevent the development of objective physiological abnormalities related to exposure to high altitude.[14] Neither acetazolamide nor dexamethasone have ever been shown to improve high altitude pulmonary oedema.[1,4] Drug treatment should never be used to permit further ascent by a patient with acute mountain sickness.

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Glossopharyngeal neuralgia associated with cardiac syncope: long term treatment with permanent pacing and carbamazepine

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Abstract

Glossopharyngeal neuralgia associated with cardiac syncope developed in a 53 year old man. Symptoms were controlled with temporary and permanent transvenous pacing and carbamazepine.

Glossopharyngeal neuralgia with syncope is a rare syndrome. It is characterised by paroxysms of unilateral intense lightning pain felt deep in the throat and pharynx, radiating to the ipsilateral ear, and associated with transient loss of consciousness caused by brief periods of asystole. Transient cerebral ischaemia may cause convulsions.

Case report

A 53 year old man was admitted in December 1976 with a two week history of recurrent syncopal attacks. He complained of a severe shooting pain in the left side of his throat radiating to the left ear, followed by dizziness and sometimes loss of consciousness lasting for a few seconds. These paroxysms had occurred several times a day and were precipitated by swallowing (mainly when drinking cold beer), chewing, brushing his teeth, and sneezing. Three weeks previously he had had non-specific "flu-like" symptoms with a productive cough, and was treated with ampicillin. He had been hypertensive for five years, and was treated with methyldopa and propranolol.

The patient was overweight and anxious. His oral hygiene was poor. His pulse was 76 per minute and regular. Blood pressure was 170/100 mm Hg. Auscultation of the heart and lungs was normal, there were no carotid bruits, and there was no abnormality of the central nervous system. Ocular fundi showed arteriovenous nipping.

During the initial clinical examination the patient had two brief attacks of pain with an intense grimace followed immediately by complete loss of consciousness. At this time the electrocardiographic monitor recorded episodes of sinus arrest with junctional escape beats (fig 1).

Glossopharyngeal neuralgia with cardiac syncope was diagnosed. Temporary bipolar ventricular pacing was established via the right subclavian vein. Over the next week the patient continued to have neuralgia but was protected from syncopal attacks by the demand pacemaker (fig 2).

Further examination of his throat showed congestion of the posterior pharyngeal wall with oedema of the uvula and tonsillar fauces. The left upper molars were loose and carious. During the dental examination the patient developed typical pain, followed by asystole which was interrupted by pacemaker intervention. A trigger zone was noted around the left peritonsillar and paramolar region, which when touched with cotton wool or ethyl chloride spray induced an attack. There was no evidence of hypersensitivity of the carotid sinus—carotid massage on either side did not produce significant bradycardia, hypotension, or asystole.[1] Somatic pain produced by squeezing the achilles tendon failed to induce an attack.

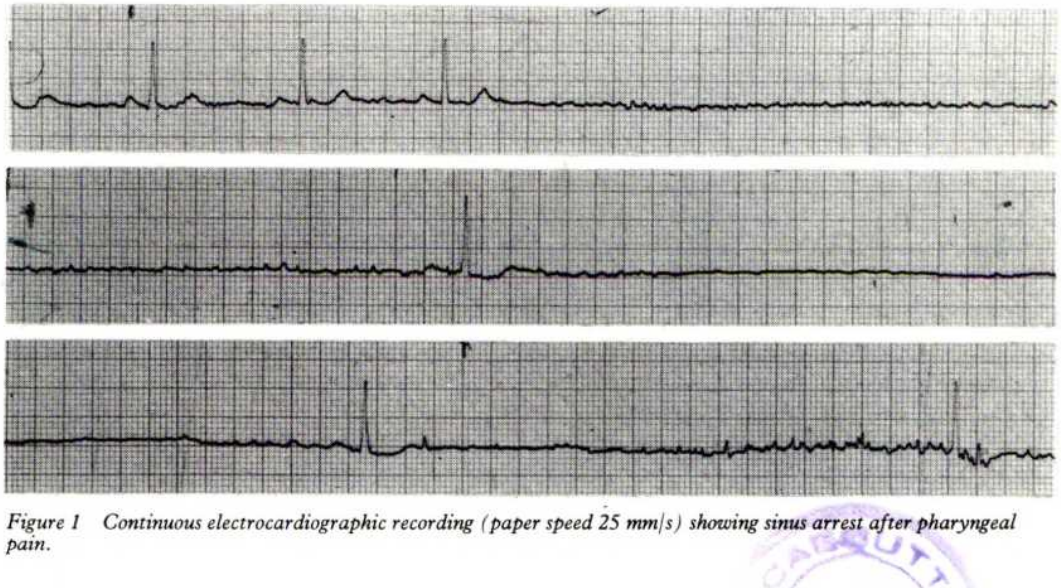

Figure 1 Continuous electrocardiographic recording (paper speed 25 mm/s) showing sinus arrest after pharyngeal pain.

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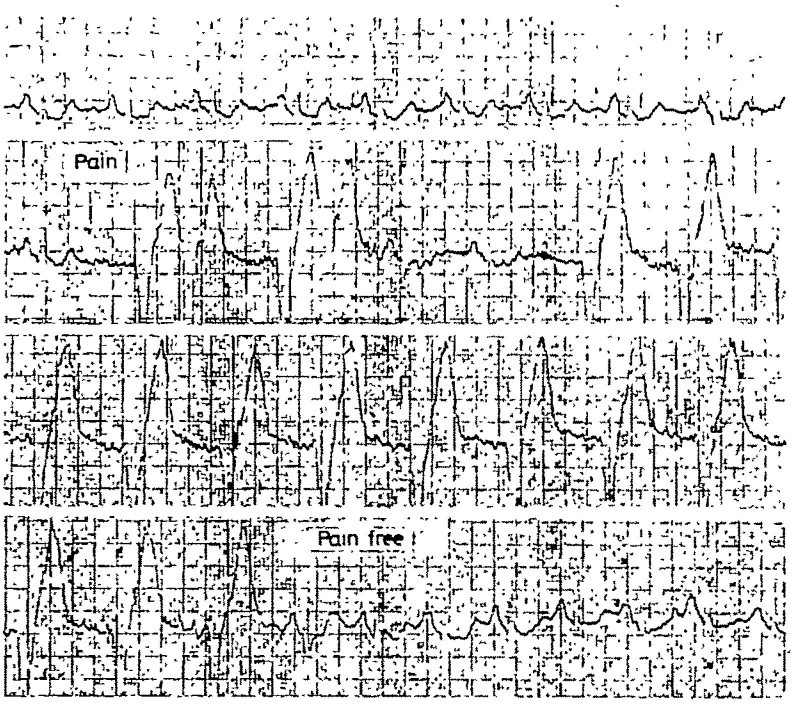

Figure 2 Continuous electrocardiographic recording (paper speed 25 mm/s) showing sinus rhythm preceding pharyngeal pain, and ventricular demand pacing during an episode of neuralgia.

Chest *x*-ray, electrocardiogram, full blood count, and blood chemistry were normal. Complement fixation tests for viruses and the Paul-Bunnel test were negative. No pathogens were isolated from a throat swab.

After a week, the patient made a spontaneous recovery. The paroxysmal neuralgia subsided completely, he stopped needing the pacemaker, and the temporary pacing electrode was removed. There was no immediate recurrence in his symptoms or any residual electrocardiogram abnormality.

He remained well and symptom free for 3 years but presented again in 1979 with further attacks of severe glossopharyngeal neuralgia, again with syncope. Temporary ventricular pacing was started and treatment with carbamazepine (1200 mg / day).

His paroxysmal attacks of pain resolved after a two week period. Because of the relapse after 3 years, we decided to continue treatment with carbamazepine and implant a permanent pacemaker to prevent syncope. Because of severe caries all his teeth required extraction. A computed tomographic brain scan was normal and subsequently a programmable VVI pacemaker was implanted.

Episodes of neuralgia pain continued infrequently over the next 5 years. He continues to take carbamazepine and was well 10 years after the implantation of a permanent pacemaker; his last attack of neuralgia was in 1987. He recognises the onset of pacing during some attacks of neuralgia and has had no syncope since the pacemaker was implanted.

Discussion

Glossopharyngeal neuralgia is rarer than trigeminal neuralgia and was first described by Weisenberg in 1910 in a patient with tumour affecting the cerebellopontine angle.[2] In 1921 Harris reported the first idiopathic case associated with syncope,[3] and Riley *et al* in 1942 reported two cases associated with syncope and seizures.[4] Several other cases have been reported. Glossopharyngeal neuralgia may be associated with trigeminal or vagus neuralgia,[5 6] hypersecretion of the ipsilateral parotid gland,[7] cerebral symptoms such as loss of consciousness and convulsions in the presence of normal heart rate and blood pressure,[8] elongation of the styloid process or calcified styloid ligament,[9] intracranial tumours and vascular abnormalities,[2 10] multiple sclerosis,[11] Paget's disease and carcinomatosis affecting the base of the skull,[12] and after dental extraction.[13]

Rushton *et al* in 1981 reviewed 217 patients with glossopharyngeal neuralgia seen at the Mayo Clinic; only four had associated syncope.[14] Lee *et al* in 1975 reviewed 17 cases of glossopharyngeal neuralgia associated with syncope.[13] Most were in patients over the age of 50 years; there was no sex difference. Most patients did not seek medical help for neuralgia until they experienced syncopal attacks. The latent period from the onset of neuralgia to that of syncope varied from a few weeks to several years. The onset of the disease is abrupt and the pain is characteristically paroxysmal, unilateral, following the path of the glossopharyngeal nerve distribution, and affecting the left side more frequently than the right.

The presence of trigger zones in glossopharyngeal neuralgia is less common than in trigeminal neuralgia. They are generally situated in the peritonsillar fossa of the same side, as in our patient. Carotid sinus massage is said to be ineffective in glossopharyngeal neuralgia, which distinguishes it from the hypersensitive carotid sinus syndrome.[15 16] However, Jamshidi and Masroor and Alpert *et al* described two elderly women with glossopharyngeal neuralgia with asystole and a hypersensitive carotid sinus.[17 18]

The mechanism and exact neural connections responsible for bradycardia after the neuralgic pain are still not completely understood. The most acceptable explanation is the close anatomical relation of the vagus and glossopharyngeal nerves.[19] Sensory impulses arising from the posterior pharyngeal wall reach the tractus solitarius and its nucleus in the medulla oblongata and communicate with the dorsal nucleus of the vagus through collateral fibres. The dorsal nucleus is the principal autonomic nucleus supplying parasympathetic fibres to the heart, bronchi, and abdominal viscera. The carotid sinus nerve (nerve of Hering) is an afferent branch of the glossopharyngeal nerve and conducts impulses from the carotid body and sinus to the medulla and plays an important role in the regulation of the heart rate and blood pressure. Impulses arising from irritative or ischaemic lesions in the peripheral course of the glossopharyngeal nerve may reach the tractus solitarius and then be relayed to the dorsal nucleus of the vagus through collaterals, or there may be a functional spillover of impulses via artificial motor-to-sensory synapses into the carotid sinus nerve as it travels with the glossopharyngeal nerve in the region of the jugular foramen.[16 18]

It has been suggested that neuralgic pain only of extreme severity will activate the glossopharyngeal-vagal reflex arc resulting in bradycardia, hypotension, and syncope. This may be an explanation of disparities in the latent period between the onset of neuralgia and syncope seen in the various reported cases.

The basic aim of treatment should be control of pain, which will in turn prevent reflex bradycardia and syncope. This can be achieved either medically or surgically. Local nerve blocks and spraying of the pharyngeal mucosa with local anaesthetic have been used but give only temporary relief.[16] In our patient local spray with ethyl chloride triggered an attack. In the chronic cases intracranial section of the glossopharyngeal nerve is a definitive and permanent treatment, but leaves irreversible and unwanted side effects.[20] Surgical resection of an anomalous styloid process may be possible.[9]

Treatment with anticonvulsant drugs has sometimes been successful. Phenytoin gives variable results,[7 14] but results with carbamazepine have been more encouraging,[14 21 22] though this drug may lose its effect with time.[23] Atropine and isoprenaline have been used as temporary emergency measures to abolish bradycardia but they have no effect on pain.

Khero and Mullins in 1971 described a patient treated by temporary transvenous pacemaker while waiting for surgical section of the nerve.[24] Jamshidi and Masroor in 1976 and Alpert *et al* in 1977 treated their patients with carbamazepine and permanent demand pacemakers because they also suffered from hypersensitive carotid sinus syndrome.[17 18] In our patient the carotid sinus was not hypersensitive and long term treatment with a permanent pacemaker and carbamazepine while not completely abolishing neuralgic pain had an acceptable outcome.

Idiopathic glossopharyngeal neuralgia associated with cardiac syncope is usually a self limiting disease with no reported fatal outcome. Spontaneous recovery is not uncommon but relapses may occur. We suggest that initially it should be treated with carbamazepine and a temporary demand pacemaker. If, however, the disorder is long standing, with a history of remissions and relapses, a permanent demand pacemaker combined with medical treatment should be considered as a more acceptable alternative to surgical section of the nerve.

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Br Heart J 1990;64:406–8

Rapid histological changes in endomyocardial biopsy specimens after myocarditis

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Abstract

The course and response to treatment in acute lymphocytic myocarditis are conventionally monitored by endomyocardial biopsy performed every 3-12 weeks. A patient with a short history (five days) of acute myopericarditis of unknown aetiology presented in cardiogenic shock with evidence of severe systolic dysfunction on the echocardiogram. The initial biopsy specimen showed histologically unequivocal myocarditis. Repeat endomyocardial biopsy after four days of treatment with steroids and azathioprine showed substantial histological improvement, a reduction in cellular infiltrate and myocardial necrosis, and interstitial fibrosis. Serial biopsies at 2 weeks and then 1, 2, 4, 5, 8, and 14 months after the initial biopsy showed progressive clearing of cellular infiltrate, increasing interstitial fibrosis, and compensatory myocyte hypertrophy by 4 months. At 14 months scattered lymphocytes persisted but myocyte abnormalities had resolved completely. The patient remained symptom free and systolic function was normal during this recovery period.

Early endomyocardial biopsy (within one week of diagnosis) may yield useful histological information on the response to treatment in patients with myocarditis. It may not be necessary to wait the customary 3–4 weeks to repeat the biopsy. This case shows the chronology of histological changes and emphasises that a return to normal myocardial function may precede resolution of the histological abnormalities, which may persist in part or may resolve totally after the acute episode.

In acute lymphocytic myocarditis, repeat endomyocardial biopsy is conventionally advised between 3 weeks and 3 months after diagnosis.[1-3] While post-myocarditic changes remote from the time of diagnosis have been described, the detailed time course of such changes has rarely been documented.[1,3] We report on a patient with myocarditis in whom repeated serial biopsy specimens were obtained over a period of 14 months after the diagnosis of myocarditis, allowing the changes between presentation and recovery to be examined.

Case report

An 18 year old hispanic girl presented to hospital in October 1986 with a 5 day history of shoulder arthralgia, fevers, and oral ulceration. For 3 days she had experienced vomiting, pleuritic and right upper quadrant pain, and lightheadedness culminating in an episode of presyncope. There were no other associated symptoms. The patient had previously been well and had two uncomplicated pregnancies and deliveries. She used alcohol, nasal cocaine, and marijuana on occasion. On presentation she was pale, unwell, but afebrile with a systolic blood pressure of 60 mm Hg and sinus tachycardia (118 beats/min). Jugular venous pressure was elevated to 10 cm. A third heart sound was audible. Lung fields were clear. There was no lymphadenopathy, thyromegaly, or splenomegaly but the liver was palpable 2 cm below the costal margin. Hypotension failed to improve with a fluid challenge and treatment with dopamine 6 μg/kg/min was started. Investigations included white cell count 11·2 10^9/l (normal 4–11 10^9/l) with a normal differential count. The erythrocyte sedimentation rate, platelet count, and serum electrolytes and creatinine were normal. The serum concentration of aspartate transferase was 318 IU/l (<35 IU/l), serum alanine transferase was normal, creatine kinase was 680 IU/l (<215 IU/l) (with the cardiac derived fraction representing 6% (0-3%)), and lactate dehydrogenase was 1758 IU/l (<537 IU/l) with a hepatic/skeletal muscle fraction of 29% (5-16%).

The electrocardiogram showed junctional trigeminy interspersed with sinus tachycardia, and left bundle branch block. An electrocardiogram 3 days later showed low voltage sinus tachycardia, poor precordial R wave development, ST elevation anteriorly, and ST depression laterally. Chest *x* ray showed blunting of the right costophrenic angle, a normal heart size and contour, and clear lung fields. The left ventricle was diffusely hypokinetic on cross sectional echocardiography with an end diastolic diameter of 4·3 cm (3·7-5·7 cm), end systolic diameter of 3·6 cm (<3·2 cm), and evidence of reduced fractional shortening (16%) on the M mode echocardiogram. There was a small pericardial effusion. Cardiac valves and wall thickness were normal. A Swan–Ganz catheter was inserted and the right atrial pressure was 9 mm Hg, pulmonary capillary wedge pressure 13 mm Hg, and cardiac output 3·9 l/min on dopamine.

An endomyocardial biopsy specimen (haematoxylin and eosin stain) showed a dense lymphocytic infiltrate with some plasma cells and eosinophils and myocyte necrosis (fig 1). No viral inclusion bodies, giant cells, granulomas or Aschoff bodies were seen. Specific stains for amyloid protein and iron were negative. The patient was treated with methylprednisolone 500 mg/day followed by a tapered dose of oral prednisone and azathioprine (75 mg/day). Despite runs of supraventricular tachycardia and second degree Wenckebach phenomenon during the initial 24 hours, the patient was symptom free. Dopamine was stopped by day 5. A repeat echocardiogram after 48 hours of treatment showed return of systolic function to normal (fractional shortening 29%) and pericardial fluid was no longer in evidence. A repeat endomyocardial biopsy after 96 hours of treatment showed greatly reduced cellular infiltrate, myocardial necrosis of a lesser degree, and the new appearance of fibrosis and granulation tissue (fig 2A, table). Serum lactate dehydrogenase and creatine phosphokinase concentrations became normal after 4 days.

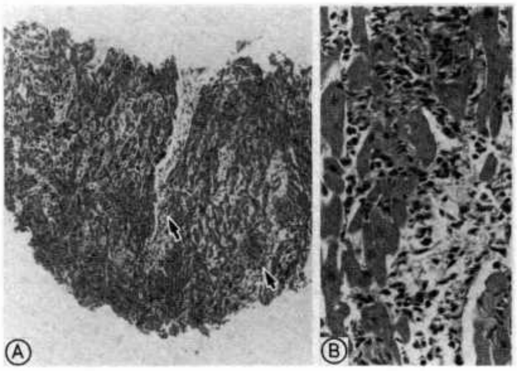

Figure 1 Endomyocardial biopsy specimen obtained on day 0. (A) The first biopsy showing a diffuse infiltrate (arrows), predominantly of lymphocytes, with myocyte damage (B) (haematoxylin and eosin, original magnification, ×80; inset ×320).

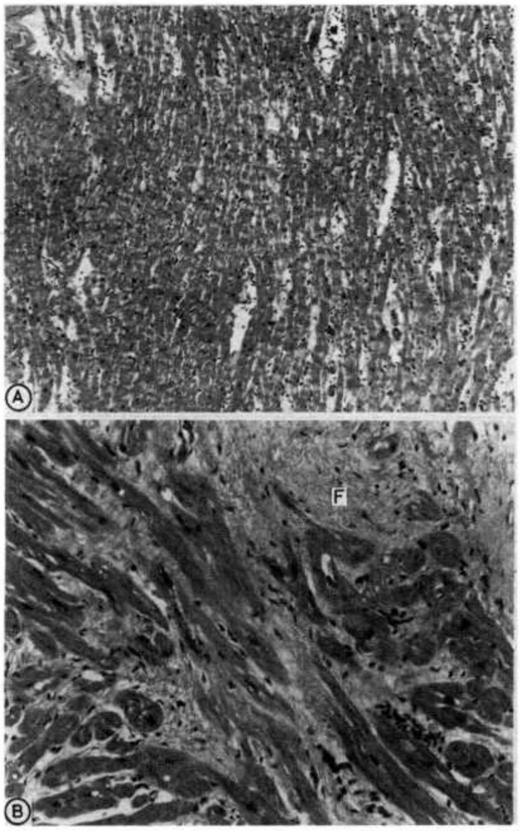

Figure 2 Endomyocardial biopsy specimens obtained on day 4 (A) and in month 4 (B). The second biopsy (A) showed reduced infiltrate (haematoxylin and eosin; original magnification, ×80). (B) A biopsy specimen taken 4 months after the initial biopsy showed interstitial fibrosis (F) with compensatory hypertrophy of the myocytes (haematoxylin and eosin, original magnification, ×100).

Histological changes with time

*Day**	*Biopsy changes*
0	Lymphocytes, plasma cells, eosinophilic infiltrate, myocyte necrosis
5	Focal lymphocytic infiltrate, less myocyte necrosis, granulation tissue, fibrosis
16	Rare eosinophils, fibrosis
39	Focal lymphocytic infiltrate, fibrosis
59	Focal lymphocytic infiltrate
111	Focal lymphocytic infiltrate, fibrosis, myocyte hypertrophy
158	Interstitial fibrosis, myocyte hypertrophy
229	Interstitial fibrosis, myocyte hypertrophy
425	Rare lymphocytes only

*After diagnosis.
Treatment with methyprednisolone and azathioprine was started 24 hours after the initial cardiac biopsy.

The cause of the myocarditis was not ascertained. Viral cultures of blood, sputum, and urine were negative as were serological tests for hepatitis A and B. Epstein–Barr testing was consistent with a past but not recent infection, and streptozyme titre, antinuclear antigen antibody, and rheumatoid factor were all negative. The serum concentration of angiotensin converting enzyme inhibitor was normal. Coxsackie, cytomegalovirus, and echovirus titres were not measured. Culture of a lower lip lesion grew the herpes simplex virus (type 1).

At discharge the patient was taking daily doses of prednisone (0·35 mg/kg) and azathioprine (1·8 mg/kg) and no specific cardiac medications. Treatment was well tolerated and doses were tapered off to stop at 6 months. She remained symptom free. Pregnancy (not advised) was confirmed 14 months after diagnosis and a normal gestation and delivery ensued.

Six further myocardial biopsies (all without complication) were performed over the ensuing 14 months and showed persistence of nonspecific fibrotic changes and development of myocyte hypertrophy by 4 months (fig 2B, table). Echocardiography continued to show a normal chamber size and systolic function. She remained clinically well 3 years after the initial episode.

Discussion

This patient is of interest in several ways. Firstly, unequivocal biopsy evidence of myocarditis was obtained and immunosuppressive treatment was started within 10 days of the onset of symptoms. Despite considerable myocardial dysfunction at presentation, clinical improvement occurred within 24 hours of the start of treatment. Echocardiographically defined systolic dysfunction reverted to normal by 48 hours, consistent with reduction in myocyte necrosis. Notable points are the rapid development of interstitial fibrosis (within 96 hours) and the early improvement seen in myocardial damage. Despite persistence of a focal lymphocytic infiltrate, fibrosis, and myocyte hypertrophy, systolic function remained normal and the patient remained well.

Acute inflammatory lymphocytic myocarditis can be subacute, recurrent, or chronic. In some patients normal myocardial function is restored and others progress to chronic dilated cardiomyopathy.[1 4 5] The role of immunosuppression is unclear—improvement in treated and untreated patients was similar in some studies and in others improvement followed treatment.[2 3 5 6] Up to 40% of treated patients improve, some returning to normal function, while the remainder die or progress to a chronic dilated cardiomyopathy.[3] Spontaneous improvement was noted in virtually all series. There is circumstantial evidence in our patient that immunosuppressive treatment may have been beneficial and the response rapid.

Progression of histological changes from those of acute inflammatory lymphocytic myocarditis to interstitial fibrosis, reduction in inflammatory infiltrate, and development of myocyte hypertrophy were reported within 4 weeks of initial diagnosis in treated and untreated patients.[1] In general, repeat biopsy is advised between 3 weeks and 3 months after the start of treatment.[2] We know of no reports of biopsy as early as 4 days. We found not only a reduction in lymphocytic infiltrate but also the development of granulation tissue and fibrosis within this short period. This indicates that earlier myocardial biopsy, even within the first week, may show improvement. Myocyte damage was only evident on biopsy specimens taken in the first 14 days. Myocyte hypertrophy was not evident until almost 4 months after the initial biopsy. By 14 months, however, the histological appearance of the specimen had returned to normal and no further biopsies were performed.

The lack of relation between the histological severity of myocarditis and clinical outcome has been commented upon before.[3] In our case too myocardial function was normal despite persisting histological abnormalities. Myocyte hypertrophy, a feature known to be associated with a better prognosis, may have had a favourable influence in this case. Resolution of histological features may lag behind recovery of function.

A repeat biopsy within a week of the start of treatment may give useful histological information in some cases of myocarditis, particularly where there is clinical improvement and non-invasive evidence of improved cardiac function. The histological appearance after myocarditis can return to normal even after relatively long periods of follow up.

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LETTERS TO THE EDITOR

- *The British Heart Journal welcomes letters commenting on papers that it has published within the past six months.*
- *All letters must be typed with double spacing and signed by all authors.*
- *No letter should be more than 600 words.*
- *In general, no letter should contain more than six references (also typed with double spacing).*

Time of occurrence, duration, and ventricular rate of paroxysmal atrial fibrillation: the effect of digoxin

Sir,—I read with interest the excellent study of Rawles *et al* (1990;63:225–7) on the effect of digoxin in paroxysmal atrial fibrillation. It is always a pleasure to see widely held beliefs about a commonly used drug overturned by careful clinical observation. I would, however, take issue with one statement in their paper. Rawles *et al* point out that digoxin shortens the refractory period of atrial muscle, rendering the atrium more susceptible to fibrillation and increasing the rate of fibrillation. They suggest that the result of the use of digoxin in atrial fibrillation is "a compromise between increased fibrillation rate and reduced atrioventricular conduction, with the beneficial effect of reduced conduction generally predominating."

In fact, the increase in atrial rate produced by digoxin may be *beneficial* in controlling ventricular response by increasing anterograde concealed conduction. The clinical existence of an increased atrial rate causing a decreased ventricular response is often noted when atrial flutter with 2:1 anterograde conduction converts to atrial fibrillation, when the increase in atrial rate results in a decreased ventricular rate.

Before conversion to sinus rhythm there is a coarsening in fibrillatory waves associated with a decrease in the number of wavelets in the atrium.[1] Experimentally this is associated with an increase in ventricular response[2]—an observation we have noted clinically.[3] Indeed, not only may the effect of digoxin on atrial refractoriness be salutary for ventricular rate control, but some investigators have suggested that it is the predominant mechanism by which the drug slows the heart rate in atrial fibrillation.[4]

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The electrocardiogram does not reliably reflect the (anatomical) transmural extent of myocardial infarction

Sir,—Metcalfe and colleagues (1990;63:267–72) presented an excellent six year follow up report of patients admitted to the coronary care unit with acute chest pain. The study was a well executed, retrospective investigation with useful results that accorded with our own recent observations. I wish to object to one small, but conceptually rather large, point. Metcalfe *et al* repeat a chronic affliction of cardiologists—the continual muddling of *anatomical* subendocardial or non-transmural infarction and *electrocardiographic* non-Q wave infarction. It is well established that the electrocardiogram cannot reliably distinguish the anatomical mural extent of acute myocardial infarcts.[1 2] Most Q wave infarcts are indeed anatomically transmural and some non-Q wave infarcts are anatomically non-transmural (mapping identifies additional Q wave zones in some "non-Q" infarcts in 12 lead recordings).

On page 270 Metcalfe *et al* refer to "non-transmural infarction as we define it", but nowhere does the text give an explicit definition; one must assume that they refer here, as elsewhere, to non-Q wave infarcts. In any case, confounding "non-transmural" or "subendocardial" with non-Q wave infarcts would be but a terminological quibble if it did not confuse concepts. The electrocardiogram is competent only to tell us if an infarct does or does not produce Q waves or other QRS changes.[2] We should therefore describe electrocardiographic results—the basis of Metcalfe *et al's* article—precisely as what is recorded, distinguishing clearly what we can see from what we may infer. The knowledgeable reader will know the range of inferences for any datum and the less well informed will be protected from unwarranted conclusions.

Finally, it was not surprising that Metcalfe *et al* did not see "convergence of survival curves in the non-Q wave group" which had a lower mortality. They reasonably attribute this to the smaller infarcts associated with Q wave absence. Would they additionally comment on the convergence of late survival curves in the early reports distinguishing Q wave from non-Q wave infarction? Since that time has treatment advanced sufficiently to account for the divergent ultimate survival? Were Metcalfe *et al's* non-Q wave patients managed more vigorously with β blocking and calcium blocking agents or other treatments than would have been the case at the time when convergence of survival curves was reported?

These remarks are meant not so much as criticism but rather to amplify and clarify an excellent study.

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BOOK REVIEW

Pearls and Pitfalls in Electrocardiography. Pithy, Practical Pointers. Henry JL Marriott. (Pp 157; £12.62.) Philadelphia and London. Lea and Febiger, 1990 ISBN 0-8121-1334-9.

Those who roam the vast exhibition areas at the major American cardiological meetings will certainly have encountered Dr Marriott at one of the booths, presenting material much like that contained in this book to a group in an open lecture theatre; they will have heard his light, yet earnest, admonitions about how much you can learn from careful scrutiny of electrocardiograms. Some of course may have read his larger books and already know of his original, sometimes idiosyncratic, yet always thoughtful, ideas. Until quite recently he would return to England every year or two and give a series of courses in London and the provinces. He makes a point of including nurses and technicians in the audience he aims to attract and always gives good value. The present book is no exception.

The first part of the title is drawn from an Oslerian phrase: "pearls are burrs that stick in the memory" and casts no aspersions on his readers. There are 70 sections, each covering one aspect, usually specific, occasionally general. Some of these segments are as brief as five lines but a few occupy more than one side of a page. Usually, but not invariably, the corresponding illustrations are opposite the text, so there is quite a lot of blank space. The individual items are important and the explanations usually, but not always, lucid. Occasionally a favourite phrase could have been less elegant but easier to understand, such as the heading for figure 39: "Anterograde conduction impaired by antecedent anterograde concealed conduction," which takes a lot of working out. But most of the points are discussed in a helpful manner, and some of the pearls are true gems, like the very appropriate explanations of parasystole and atrioventricular dissociation. Occasionally Marriott uses the author's privilege to trot out a hobby horse, an example being his personal definition of high grade block.

Many statements are supported by references and he sometimes highlights classic observations that deserve recall. Others, like the estimation of right ventricular pressure from V1, are unsupported. But his favourite source of wisdom is Sherlock Holmes, which gives you an idea of his approach. You will have to follow the master, too, when working out the numbering of the figures; the first is figure 2, a little disconcerting until you realise that each figure corresponds to a numbered item of text.

Worth while? Very definitely: an ideal Christmas present to the medical and nursing staff of a coronary care unit—excellent for systematic reading or for the occasional brief glance. And if you attend an American conference and hear that Barney Marriott is giving an extramural presentation, don't miss it either. He is excellent on the rostrum, and this book gives you the flavour.

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Br Heart J 1990;64:410

BRITISH CARDIAC SOCIETY NEWSLETTER

Stockholm is now a memory. Was it a popular venue? Some complained that the hotels were very scattered, but few cities could accommodate so many visitors to a conference within easy reach of the conference centre. What a pity that London is not able to host the annual scientific sessions of the European Society of Cardiology; no doubt many other organisations would like to meet in London if we had adequate facilities for large gatherings. The organisation at Stockholm was excellent. There is a clear advantage in the same group having similar responsibilities from year to year so that learning curves are not repeated. Representation from the United Kingdom was good (a total of 707 registrants) but this presumably included not only cardiologists but also exhibitors and spouses. Flights to Sweden became very difficult to book in the week or so before the conference: here is a lesson that might be learned for another day. We record with particular pleasure that two of the three named lectureship series of the European Society were given by British colleagues—both closely associated with the *British Heart Journal* as Editor and Assistant Editor. Dennis Krikler gave the Henri Denolin Lecture entitled "The development of electrocardiography in Europe: a century of progress". Michael Davies gave the Andreas Gruntzig Lecture on "Acute ischaemic syndromes: the morphological basis". In addition, Andrew Henderson was one of the invited lecturers on heart failure in the Joint American College of Cardiology/European Society of Cardiology Symposium.

We return to the subject of audit. (Please do not stop reading the newsletter at this point.) We all believe in audit, appreciate its value, and recognise that we did not have enough of it previously. We no doubt suspect that we have too much of it now We are assailed from every direction: district, regional, and national groups all demand our participation. We are aware of three separate initiatives to audit the management of acute myocardial infarction. We hope the joint College and Society Audit Committee can keep a measure of control over events, for otherwise the understandable reaction will be to wish to avoid cooperating with any of them. Eventually we will achieve a sensible level of useful activity, but for the moment audit often seems an end in itself rather than a tool to improve performance. We are unfamiliar with many of its concepts, and so participation does not come naturally. Out own committee has several projects now under way, and has ensured that they are not overambitious. A pilot study is examining delays in the treatment of acute myocardial infarction with participation at present of only five district general hospitals. Another pilot study is examining the complications of coronary angiography in a few major centres—useful lessons will surely follow The intention is to spread the net more widely for both of these inquiries as experience with them grows.

One form of audit that has been discussed is based on visits by one cardiologist to a colleague in another centre. The audit committee encourages this practice, but it must occur with willing cooperation from both sides. The major centres already have their inspections from the Specialist Advisory Committee, so the less formal visits are intended for district general hospitals. Visits may either be unstructured and based on impressions rather than on the collection of hard data or structured, with performance indicators that can be used for comparisons between centres or to monitor change within any one centre. The audit committee will not at present be directly involved with these visits, which will generate very large volumes of data that will be difficult to analyse. We hope, however, that visits will take place as a result of local initiatives. They were pioneered in the South East Region by Richard Wray before audit became fashionable, and they have proved to be popular. Recently visits have occurred across regional boundaries and have been equally successful. The audit committee does have suggestions for inquiries that could form the basis of a structured visit. A questionnaire headed "Organisational Medical Audit" has been prepared; it comprises sections on outpatient audit, inpatient audit, and investigation audit—a total of 34 questions. The document can be sent in advance to the cardiologist who is to be visited so that he or she has advanced notice of the topics that will be raised. It is intended as a model to be used in its entirety, or in part, or to generate the determination to do something quite different. Having a format of this type does, however, overcome the potential difficulty of a visiting cardiologist having to seek guidance on what he should be doing. Those participating will quickly appreciate that two districts are being audited at once: the visitor will find he is reflecting on practice in his own unit, and discussing differences with his colleague, usually to mutual advantage. If you wish to have a copy of the questionnaire please contact Nicholas Brooks at Wythenshawe—he is chairman of the audit committee. But he will not want the document back when it is completed: the data are for local use only. Structured visits to district general hospitals will eventually become more formal, particularly for those participating in specialist training by having rotating registrar posts in cardiology.

Many readers will have known Dimitri de Grunwald, and will have been saddened by his death in May. Dimitri had his first career in pharmaceuticals, and was a managing director by the age of 30. He later joined his elder brother to produce films of outstanding merit with personalities such as Peter Sellers and Sophia Loren. But in the last nine years of his life he embarked on a new career as a consultant to Bayer. With the full support of the company, he developed a new concept in workshops that were attended by many of the senior academic cardiologists in Britain. The formula was good preparation, an attractive venue, the most friendly of atmospheres, but above all the expectation of hard and productive work. Dimitri and his workshops both became institutions. His memorial service at the Russian Orthodox Church in Kensington was attended by cardiologists from many parts of the United Kingdom as well as by colleagues from abroad and by friends from other walks of life. A moving tribute has been written by Professor Gus Born. It is much too long to be reproduced here, but a brief extract may provide the flavour: "Underlying all was Dimitri's phenomenal good nature: phenomenal because it came, not with blindness to life's unpleasantness but, on the contrary, with the ability to understand people's problems only too well." And so indeed he did. Copies of the tribute are available on request for any of his friends who might like one· please write to Elaine Brown at the British Cardiac Society. The tribute gives a vivid impression of a remarkable man who made his own very special impression on British cardiology.

DOUGLAS CHAMBERLAIN
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NOTICES

British Cardiac Society
The Annual Meeting will take place at the Scottish Exhibition Centre, Glasgow on 30 April to 3 May 1991. The closing date for receipt of abstracts will be 10 December 1990.

Hypertrophic Cardiomyopathy Association
This recently established patient-based charity aims to provide information and support for patients and their families and to increase public awareness of the condition. The Association is supported by a medical advisory subcommittee. Inquiries to the Hypertrophic Cardiomyopathy Association, 44 Minerva Road, Park Royal, London NW10 6HJ. Telephone 081 963 0020.

Intensive care and emergency medicine
The 11th International Symposium on Intensive Care and Emergency Medicine will be held in Brussels on 19 to 22 March 1991. Further information from Professor J L Vincent, Department of Intensive Care, Erasme University Hospital, Route de Lennik 808, B-1070 Brussels, Belgium.

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The first major book devoted exclusively to this widely used diuretic agent.

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BUMETANIDE

Brief Contents

Historical background, taxonomy and chemistry

Pharmacology of bumetanide

Pharmacokinetics and pharmacodynamics

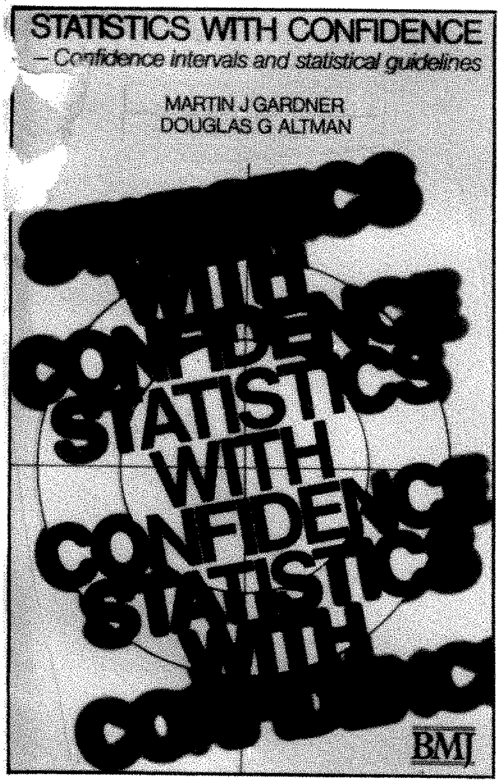
Clinical indications

Contraindications, adverse effects and toxicity

Bumetanide in combination with other agents

Bumetanide dosages and formulations

• BUMETANIDE •



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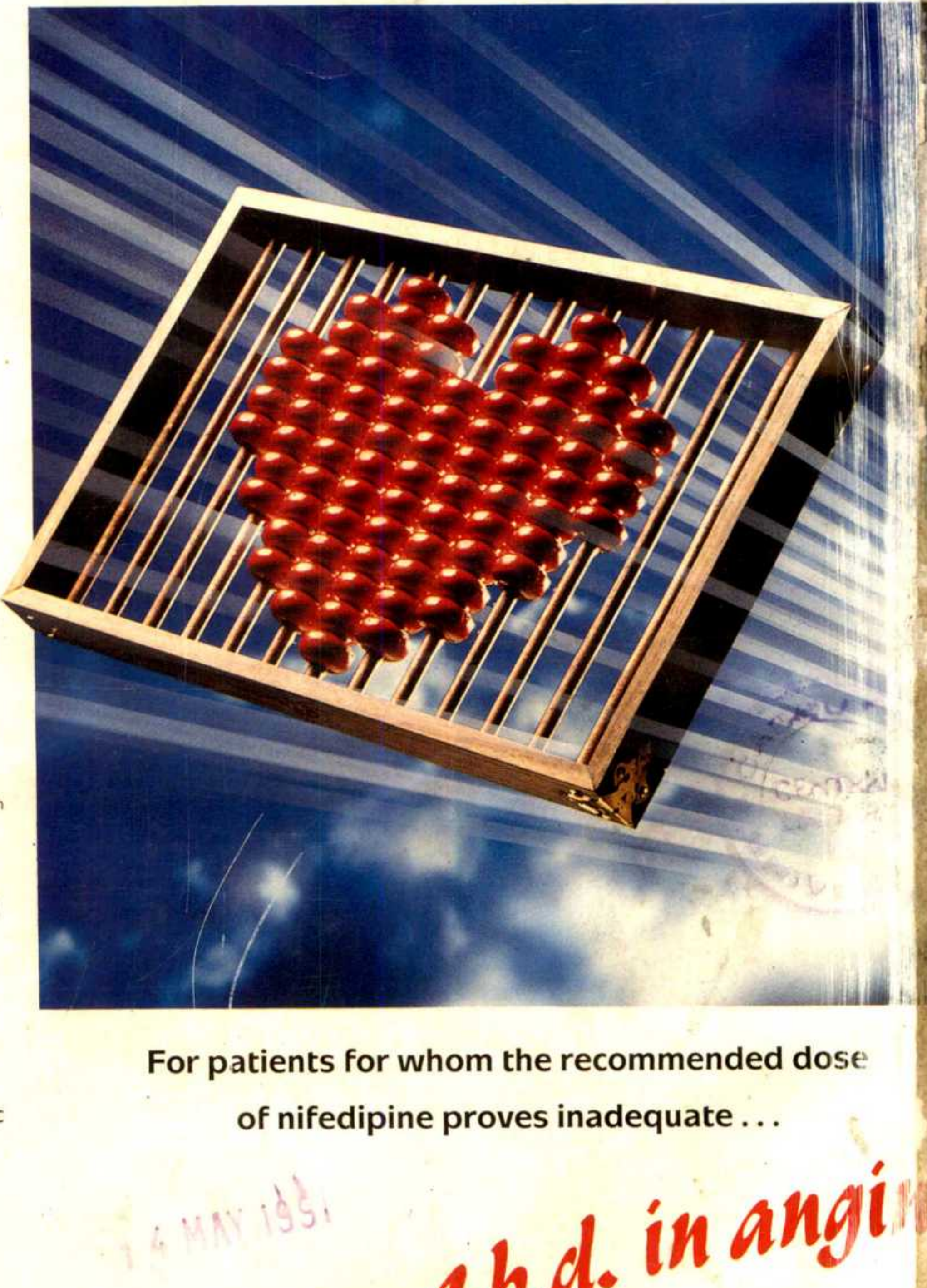

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